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Dr. Rowe initiated a capability in clinical microbiology at BNW in 1975 and has supervised this function since that time. He has had the responsibility for and much experience in the preparation of barrier procedures for the exclusion and control of infectious agents. During his 20 years at Battelle, he has provided guidance and oversight for the varied animal care and use activities at the Laboratory.

Dr. Rowe will closely monitor the health of the animals assigned to these studies and will interact with the PI, the Animal Resources and Toxicology Staff, and other personnel assigned to the studies to assure that feed and water quality, sanitation, barriers and environmental conditions are properly maintained. He will also monitor the quality of animal care activities and ensure compliance with animal welfare regulations.

8. Health and Safety Officer–J.Y. Young

Mr. John Y. Young received his BS degree in Preventive Medicine in R and his MS degree in Public Health (Industrial Hygiene) in R both from the University of Washington, Seattle, WA. Mr. Young is a Diplomate of the American Academy of Industrial Hygiene, certified in the Comprehensive Practice of Industrial Hygiene;

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Before joining Battelle, Mr. Young had spent 20 years with the U.S. Army as an Environmental Science Officer specializing in industrial hygiene.

Mr. Young is responsible for the planning and execution of an Environmental, Safety, and Health (ES&H) Program in support of the research contracts related to chemical exposures. Mr. Young represents the Toxicology Department on ES&H issues, and ensures that all research activities are in compliance with OSHA, EPA, and other relevant regulations. Additionally, Mr. Young is also involved in individual research projects within BNW, working on toxicologic evaluation and exposure assessment of potentially hazardous vapors in underground storage tanks on the Hanford site.

Mr. Young will oversee the proper planning and execution of an ES&H program in support of the proposed research program, and provide input to research scientists in industrial hygiene evaluation and control, workers' protection, and environmental pollution prevention.

9. Quality Assurance Officer–R.A. Gelman and M.G. Horstman

Ms. R. Ann Gelman supervises the activities of the QA Unit. She reports directly to the Manager of Operations of the Life Science Center.

a. R. Ann Gelman. Ms. Gelman received her B.S. degree in Foods and Nutrition from Carnegie Institute of Technology in R and an MS degree in Nutrition in R from the University of Pittsburgh. In her present position (QA Unit Specialist, GLP Office), she is responsible for ensuring that projects conducted under GLP regulations for nonclinical laboratory studies are in compliance with those regulations. She is also responsible to management for: 1) ensuring that the research facility is in compliance with GLP regulations, 2) auditing and surveillance activities, 3) assisting Project Managers in setting up GLP procedures and documentation for their projects, and 4) assisting auditors from clients or other agencies during facility and project inspections.

Prior to assuming the QA Unit Senior Specialist position, Ms. Gelman was, for 5 years, a Research Assistant in the Biology and Chemistry Department, assisting in studies of the toxicology of inhaled fossil-fuel-related carcinogens. Previous to that, she was a Senior Research Assistant for 8 years, supervising a group specializing in the biochemistry of trace lipids. Ms. Gelman has 12 years of experience reviewing toxicity studies conducted under the GLP regulations.

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b. Michael G. Horstman. Mr. Horstman earned B.S. degrees in Zoology and Biology in R, and an M.S. in Pharmacology and Toxicology in R Mr. Horstman was a Scientist in the Toxicology Group within the Toxicology Department for 4 years. He had previously worked 2 years as a Technical Specialist in the Biology and Chemistry Department at BNW. He has extensive laboratory experience in mammalian toxicology and the study of molecular mechanisms of toxicity, particularly metabolic activation and macromolecular adduction processes. This also includes experience in a variety of laboratory analytical methods.

In his present position, Mr. Horstman helps to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with GLP regulations. His duties include surveillance of study procedures, data audits, reviews of Final Reports, as well as assisting the Lead QA Officer during facility and project inspections from clients and other agencies.

C. OTHER SENIOR PERSONNEL

1. Dr. Richard P. Schneider

Richard P. Schneider obtained his B. S. in Biology from Kent State University and his Ph.D. in Animal Physiology from Washington State University in R He has been the manager of the Molecular and Structural Biology Section since 1980. In this capacity he has 13 years of experience in carcinogenesis and mutation research. For the past 6 years he has been using molecular biology methods to identify mutation in oncogenes and tumor suppressor genes. This includes all of the methods needed for the Blue Mouse assay including: DNA extraction, bacteria and λ phage culture, phage plaque selection, molecular cloning in phagmids, polymerase chain reactions and DNA sequencing. Dr. Schneider is well qualified to lead this task.

2. Dr. David L. Springer

Dr. Springer has a BS in General Studies (Biology and Chemistry) and a PhD in Biochemistry from the University of Idaho. Additional training as a Research Associate (post-doc) was obtained from the Department of Agricultural Chemistry at Oregon State University. Dr. Springer joined BNW in 1979 and is a Staff Scientist in the Biology and Chemistry Department.

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Dr. Springer has 15 years experience in biochemical toxicology with emphasis on the mechanisms whereby organic materials contribute to tumor development. This experience includes metabolism, metabolite isolation and structural characterization, the enzymology of Phase I and Phase II reactives, and DNA/protein adduct isolation and characterization. Currently, Dr. Springer is funded by DOE/OHER to study the influence of bulky chemical adduct for chromatin structure and gene expression. Dr. Springer will conduct the enzyme assays and participate in the protein/DNA adduct studies.

D. ADDITIONAL PERSONNEL

1. Clinical Pathology

a. Supervisor--C.O. Romsos. Ms. Claudia O. Romsos is a Technical Specialist II in the Clinical Pathology Group of the Toxicology Department. She joined the staff of BNW in April 1983. She has an AA degree from Boise Junior College R , a BA degree from Eastern Washington State University , and attended Sacred Heart Medical Center School of Medical Technology REDACTED

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Prior to joining BNW, she worked at a local hospital and in an out-patient laboratory in the Richland area (1960-1983). She has 30 years of experience and has trained in all aspects of the clinical laboratory. She functions as the Clinical Laboratory Supervisor.

Name	Title	Areas of Responsibility	Years of Experience
DL Redetzke	Clinical Technician; MT (ASCP)	Hematology; clinical chemistry; urinalysis; & special assays	14
KH Debban	Technical Specialist; MT (ASCP)	Hematology; clinical chemistry; urinalysis; & special assays	24
SL Martell	Technical Specialist; MT (ASCP)	Hematology; clinical chemistry; urinalysis; & special assays	14
AE Jarrell	Technical Specialist; MT (ASCP)	Hematology; clinical chemistry; urinalysis; and special assays.	14
MM Jones	Technician	Blood collection	6
CM Abraham	Technician	Blood collection	2
JJ Wodtli	Technician	Blood collection	1

2. Program Administration

a. Department Administrator--P.S. Ruemmler. Ms. Patricia S. Ruemmler is the Department Administrator for the Toxicology Department. She received her BA degree from Mills College, Oakland, CA, with a major in Biology. Ms. Ruemmler is responsible for monitoring financial and contractual performance, including tracking contract modifications and updating/revising the work breakdown structure. She maintains milestone schedules and assists the PI in keeping Line Management and the Sponsor informed of potential or existing problems with those schedules. She coordinates all technical and business requests for proposals with the technical staff, BNW finance, and contracts departments. Ms. Ruemmler is responsible for supervising all the activities of the Inhalation Toxicology Program Office. These activities include records management, coordination of monthly reports, maintenance of milestone and deliverable schedules and the archiving and shipping of study data. Prior to assuming this position, she served as a QA Auditor in the GLP QA Unit of the Life Science Center where she was responsible for ensuring that projects conducted under GLP regulations for nonclinical laboratory studies were in compliance with those regulations. She has worked at BNW since 1972 and has an extensive background in many technical areas. Prior to that she was a technician in the Molecular and Cell Biology Section of the Biology and Chemistry Department for 7 years where she assisted on narcotic antagonist studies, iron chelating studies, and on numerous metabolism studies on actinide absorption in both adult and neonatal rats, dogs, guinea pigs and Hanford miniature swine.

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Name	Title	Areas of Responsibility	Years of Experience
AM Busselman	Administrative Assistant	Financial support, updating monthly budgets and cost details; maintaining labor matrices and other project management spread sheets	4
LJ Eberhart	Senior Clerk	Typing, mailings, duplicating, and general clerical support for staff	6
ME Mericka	Sr. Administrative Assistant	Document processing, recordkeeping, technical editing, and report compilation	14
BJ Van Zandt	Sr. Administrative Assistant	Generating milestone schedules; monitoring study events; archiving study records; records management; coordinating Monthly Report	8

3. Toxicology

a. Lead Specialist--J.T. Pierce. Ms. Judy T. Pierce is a Technical Specialist III in the Inhalation Toxicology Technical Group within the Toxicology Department. She joined Battelle in the Animal Resources Group in 1977, and was promoted to Technical Specialist in 1987. She earned her Bachelor's degree from the University of Idaho in REDACTED REDACTED REDACTED. As Lead Technical Specialist, she is responsible for training and supervising other Toxicology Technical Specialists and Technicians in the Inhalation Toxicology Technical Group. Routinely, she monitors study progress, performs in-life clinical observations, and reviews in-life data printouts. She also assists in protocol, SOP, and study report preparation.

Name	Title	Areas of Responsibility	Years of Experience
DL Bove JC Blessing TM Luders	Toxicology Specialists	Supervise & train technicians; coordinate schedules; prepare SOPs & reports; perform in-life clinical observations & review in-life data	7 6 5

4. Xybion Path/Tox Computer Software

a. Assistant System Manager--J.C. Blessing. Mr. John C. Blessing is a Technical Specialist II in the Inhalation Toxicology Technical Group within the Toxicology Department. He joined BNW in the Animal Resources Group in 1986 and was promoted to Technical Specialist in 1989. He earned his BA degree from Washington State University in REDACTED REDACTED REDACTED REDACTED

Mr. Blessing has 7 years of experience with the Xybion Path/Tox computer software and has participated in a variety of capacities in data collection. He is currently the designated Assistant System Manager. As the Assistant System Manager, he assigns operator privileges, trains and assists technicians, toxicologists, and pathologists in their use of the software, and assumes overall responsibility for records maintenance, general diagnostics and remediation, software validation, and correspondence with Xybion Medical Systems.

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5. Animal Resources

a. Supervisor--A.P. Wagner. The Animal Resources Group is lead by Ms. Alison P. Wagner. Ms. Wagner has an Associate of Science in Veterinary Technology degree from Pierce College. She has 6 years of experience in laboratory animal care at BNW. Ms. Wagner has been LSL-II Animal Resources Supervisor since August 1992 and prior to that, was Assistant Supervisor for the facility for 2 years. Before that, she was an Animal Resources Specialist. Her duties include supervising and training technicians, coordinating schedules, directing facility maintenance and animal care, and preparing SOP's and reports.

Ms. Wagner supervises the activities of 24 technicians. Six of these people have 17 or more years of experience in laboratory animal care at BNW. Seven of these individuals are American Association of Laboratory Animal Science (AALAS)-certified Laboratory Animal Technicians; two are AALAS-certified Assistant Laboratory Animal Technicians.

The Animal Resources Staff provide for the daily care and routine daily observation of the animals. They also interact closely with the toxicology staff and the exposure staff. They assist with the collection of clinical observation and weight data; tattoo the animals; maintain sanitation throughout the facility; and wash and changeout racks, cages and related equipment.

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Name	Title	Areas of Responsibility	Years of Experience
VL Dedmond	Senior Animal Technician	Daily check for moribundity & mortality; daily animal husbandry procedures; animal facility sanitation; clinical observations; body weights	27
GL Miller	Senior Animal Technician		25
PA Pierce	Senior Animal Technician		18
DC Snyder	Senior Animal-Technician		19
FL Wallace	Senior Animal Technician		25
CM Abraham	Animal Technician		2
JE Caldwell	Animal Technician		1
SW Chase	Animal Technician		1
MS Cockburn	Animal Technician		1
JT Dvorak	Animal Technician		5
SF Harris	Animal Technician		5
MM Jones	Animal Technician		6
DR Kimsey	Animal Technician		9
JP Rogers	Animal Technician		20
MA Skogley	Animal Technician		8
SL Stewart	Animal Technician		1
SA Webb	Animal Technician		2
JJ Wodtli	Animal Technician		1
SA Breier	Animal Technician (new hire)		1
EO Cox	Animal Technician (new hire)		1
B Gillard	Animal Technician (new hire)		1
CR Helland	Animal Technician (new hire)		1
PM Kopf	Animal Technician (new hire)		1
JW Short	Animal Technician (new hire)		1

6. Veterinary Services

a. Veterinary Service Specialist–K.H. Debban. The animal health program is directed by Dr. S.E. Rowe, REDACTED Dr. Rowe is supported in the laboratory by Ms. Kathryn H. Debban, REDACTED with 24 years of experience in medical technology. She has worked as a medical technologist for BNW since 1975 and has worked in the veterinary services diagnostic laboratory since January 1991.

Also available on a call-in basis is Ms. Kimberly G. Pauly. Ms. Pauly is also an REDACTED REDACTED She has 6 years of experience in medical technology.

Both Ms. Debban and Ms. Pauly are experienced and qualified to do serological testing for viral antibodies, culture and identification of bacterial pathogens, and water culture and monitoring techniques. They are involved with nearly all aspects of the health care program including preexposure health screening, testing sera for viral antibodies, drinking water quality monitoring, and report preparation. The veterinary services laboratory participates in the Rockefeller University QA program in serology and bacteriology for laboratory animal diagnostic laboratories.

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7. Pathology

a. Necropsy and Histology Supervisor--K.M. Gideon. Ms. Katherine M. Gideon is a Senior Technical Specialist in the Pathology Group of the Toxicology Department. She joined the staff of BNW in October 1980. She has an AA degree from Spokane Falls Community College REDACTED REDACTED REDACTED REDACTED) in the field of histology. and has presented several posters, workshops and lectures at state and national meetings in the field of veterinary histology and techniques.

Prior to joining BNW, she worked at Sacred Heart Medical Center, Spokane, WA (1976-1977), Pathology Associates, Spokane, WA (1977), and Washington Animal Disease Diagnostic Laboratory, Washington State University - Pullman, WA (1977-1980). She has 16 years of experience in histology and has trained in all aspects of technical procedures of histology and necropsy. She functions as the Histology Laboratory Supervisor in coordinating efforts with histology/necropsy technicians in performing the duties of necropsy, trimming, slide preparation, and repository shipping.

Name	Title	Areas of Responsibility	Years of Experience
SM Baze	Necropsy Supervisor	Necropsy; IANR data entry & review	13
TA Breier	Histology/Necropsy Tech.	Histology/necropsy technicians are cross-trained and able to perform duties in both areas (histology & necropsy) depending on the situation.	9
AL Reed	Histology/Necropsy Tech.		2
TS Bisson	Histology/Necropsy Tech.		2
RF Flores	Histology/Necropsy Tech. HT (ASCP)		19
HW Hill			6
MD Littleton	Histology/Necropsy Tech.		3
BG Moore	Histology/Necropsy Tech.		19
MA Pope	Histology/Necropsy Tech. HT (ASCP)		11
SJ Schmaljohn			2
JD Stearns	Histology/Necropsy Tech.		21
KG Studnicki	Histology/Necropsy Tech.		2
RM Fairweather	Histology/Necropsy Tech.		3
LA Wisse	Histology/Necropsy Tech.		2
NS Marvin	Histology/Necropsy Tech.		1
JL Darnell	Histology/Necropsy Tech.		1
SV Hall	Histology/Necropsy Tech.		1
WA Holstein	Histology/Necropsy Tech.		1
DA Millman	Histology/Necropsy Tech.		1
MR Moore	Histology/Necropsy Tech.		1
K Goodey	Histology/Necropsy Tech.		1
	Histology/Necropsy Tech.		1
	Histology/Necropsy Tech.		
	Histology/Necropsy Tech.		

8. Chemistry

a. Chemistry Specialists. The Chemistry Specialists are responsible for the setup, optimization, and maintenance of a wide variety of chromatographic and spectrophotometric instrumentation. They perform first-echelon data review as well as production of Standard Operation Procedures for routine operations. They train, supervise, and schedule the activities of the Chemistry Technicians in the operation,

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maintenance, and calibration of the exposure monitoring systems and in the performance of special studies such as chemical stability studies, toxicokinetic or bioanalytical studies. The Chemistry Specialists are responsible for modification of instrumentation to perform special analytical operations (typically on-line exposure monitoring). The Chemistry Specialists coordinate routine and nonroutine tasks with other technical groups. They are responsible for assuring that Good Laboratory Practices are followed in the conduct of data collection. The Chemistry Specialists are responsible for the compilation of reports and in preparing technical input for proposals and scientific publications.

Name	Specific, Pertinent Study Experience	Years of Experience
DJ Anderson	Prechronic studies of gluteraldehyde. Prechronic and chronic studies of Ozone. Ozone on-line monitoring by UV spectrophotometer. Experienced with GC, GC/MS, ICP-AES, HPLC instrumentation and methods development. Prechronic and chronic studies of 7 vapor studies. Prechronic and chronic studies of 7 pharmaceutical studies with GC and HPLC support. Assisted with 2-butoxyethanol metabolite studies.	6
BK Hayden	Prechronic and subchronic studies on mainstream tobacco smoke. Prechronic humectant studies in support of tobacco research. Liquid aerosol studies in support of tobacco research. Sponsor submitted plasma samples for determination of nicotine and cotinine in support of tobacco research. Experience includes: exposure atmosphere assessment for nicotine, humectants, and liquid aerosols; chromatographic determination of percent carboxyhemoglobin from hamster blood; chromatographic determination of nicotine and cotinine in animal blood. Chemical constituent measurements for solvent refined coal and shale oil studies. Experience includes: chemical class fractionation; chromatographic identification and quantitation; physical properties measurements. Prechronic, subchronic, and chronic studies of 9 organic vapor studies. Prechronic study for GaAs. Prechronic, subchronic, and chronic studies of 9 pharmaceutical studies. Experienced with GC/MS, GC, LC, ICP-MS, instrumentation and methods development. Bioanalytical measurements of parent and metabolite compounds in blood and urine from animals exposed to styrene, acetone, acetonitrile, 1-nitropyrene, and furfuryl alcohol.	14
RE Hauber	Prechronic, subchronic and chronic studies of 5 inorganic dust studies. Chronic studies with biological assays for MoO_3, GaAs and Ga_2O_3 by ICP-AES and GFAAS. Experienced with ICP-AES, GFAAS/AAS, and GC instrumentation and methods development. Prechronic and chronic studies of 9 pharmaceutical studies with HPLC support. Assisted in 6 vapor studies.	7
AD Mercy	Prechronic studies of Gallium Arsenide. ICP-MS support for bioanalytical assays of lead. Experienced with IC, FAAS, ICP-AES, ICP-MS instrumentation and methods development.	14
KH Mellinger	Prechronic and subchronic studies on mainstream tobacco smoke. Prechronic humectant studies in support of tobacco research. Experience includes: exposure atmosphere assessment for nicotine. Prechronic, subchronic,and chronic studies of 6 organic vapor studies. Prechronic, subchronic, and chronic studies for 5 inorganic dust studies. Experienced with ICP-AES, GFAAS and FAAS instrumentation and methods development. Also experienced with IR, GC, UV-VIS and titrimetric methods. Bioanalytical measurements of parent compounds in blood, urine and tissues from animals exposed to GaAs, MoO_3, Ga_2O_3, CdO, and InP. Radioanalytical measurements is support of radiolabeled aerosol drug study. Experienced with Sample Oxidizer and Scintillation Counter.	8
RJ Moore	Experience in operation and applications development for the following instrumentation: GC, GC/MS, HPLC, and LSC. Experience in operation of the following instrumentation: ICP-AES, GFAAS and FAAS. Lead specialist for 2 chronic vapor studies. Assisted in 10 chronic vapor and 5 chronic dust studies. Further experience includes: analytical methods development for pharmaceuticals and pesticides, instrumentation modifications for vapor analyses, and assistance in metabolite studies.	4

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b. Chemistry Technicians. The Chemistry Technicians perform routine sample preparation and analysis following written analytical procedures. They perform data workup and routine report generation. They assist in the implementation of new analytical methods, method development and the development of procedures for special studies such as chemical stability studies, toxicokinetic, and bioanalytical studies. The Chemistry Technicians are involved in the maintenance of analytical instrumentation, maintenance of test material inventory, and procurement of necessary supplies. They are responsible for routine recordkeeping according to Good Laboratory Practices. Due to a program of aggressive cross-training, each chemistry technician is capable of performing almost every technician task. As a result, technicians are not normally assigned primary responsibility for a particular study.

Name	Specific, Pertinent Study Experience	Years of Experience
SA Barraclough	Assisted with 14 day and 3 month mainstream smoke studies in rodents. Assisted with glutaraldehyde prechronic studies. Assisted in over 12 prechronic and chronic vapor studies	20
SL Crowner	Assisted with isoprene and isobutene prechronic and chronic studies. Assisted in 6 prechronic and chronic vapor studies. Assisted in prechronic radiologic pharmaceutical studies.	2
HA Droppo	Assisted with prechronic radiologic pharmaceutical studies. Assisted in 4 prechronic and chronic vapor and dust studies.	2
BD MacIsaac	Assisted with 8 prechronic and chronic pharmaceutical studies. Assisted in 2 prechronic vapor studies.	3
LL Reed	Assisted with isoprene and isobutene prechronic and chronic studies. Assisted with 4 prechronic and chronic pharmaceutical studies.	1
KK Weitz	Assisted with isoprene and isobutene prechronic and chronic studies. Assisted with furfuryl alcohol and 2-butoxyethanol urinary metabolite studies. Assisted in 4 vapor and dust studies. Assisted in 3 prechronic and chronic pharmaceutical studies.	2

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IX. MILESTONE SCHEDULE

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IX. MILESTONE SCHEDULE

For purposes of scheduling and cost estimates, it has been assumed that the contract will be awarded January 1, 1994.

Milestones have been set to provide for adequate staffing and scheduling of the exposure rooms, exposure starts, and necropsies (shown on pp. IX-2 and IX-3). The time estimates and cost estimates are predicated on the following assumptions: ability of animal suppliers to deliver, on time, the required number of mice; on-time arrival of the test article; and final experimental design specifications and toxicologic parameters to be determined do not differ significantly from those in this technical proposal.

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PROVIDE INHALATION TOXICITY STUDIES OF CLIENTS PROPRIETARY PRODUCT
MILESTONE SCHEDULE

CONTRACT AWARD	12/31/93
CONTRACT START	1/1/94
Systems design and parts procurement	Jan-1994 (4 months)
Pilot Study	Mar-1994 (3 months)
Construction generation, distribution, monitoring and exposure systems	May-1994 (6 months)
START PHASE 1	Nov-1994
Sponsor Review/Approval Prestart Reports, order animals	May-1995
90-DAY - For-Nose Only	
START EXPOSURE	Aug-1995
TERMINAL SACRIFICES	Oct-1995
Submit Reports to sponsor	Jul-1996
Review Reports and approve carcinogenicity study	Aug-1996 (6 months)
CARCINOGENIC - For-Nose Only	
START EXPOSURE	Mar-1997
Respiratory Minute Volume	
6 Months	Sep-1997
12 Months	Mar-1998
18 Months	Sep-1998
23 Months	Feb-1999
Carboxyhemoglobin of the blood	
6 Months	Sep-1997
12 Months	Mar-1998
18 Months	Sep-1998
23 Months	Feb-1999
Nicotine and nicotine metabolites in the urine	
6 Months	Sep-1997
12 Months	Mar-1998
18 Months	Sep-1998
23 Months	Feb-1999
Particle clearance from the lungs	2 times/study
Lung Burden	
15 Months	Jun-1998
18 Months	Sep-1998
Differential blood cell count	
Terminal Sac	Mar-1999

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PROVIDE INHALATION TOXICITY STUDIES OF CLIENTS PROPRIETARY PRODUCT
MILESTONE SCHEDULE

CARCINOGENIC - For-Nose Only (continued)

INTERIM REPORTS	
12 Months	Mar-1998
18 Months	Sep-1998
TERMINAL SACRIFICES	Mar-1999
REPORT DUE	Feb-2000
Manuscripts for publication prepared and approved by sponsor and submitted to journals	Aug-2000
Archive materials submitted to sponsor	Dec-2000

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APPENDIX A

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APPENDIX A

DRAFT PROTOCOLS

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TWO-YEAR CARCINOGENICITY NOSE-ONLY INHALATION STUDY OF ROOM AGED CIGARETTE SIDESTREAM SMOKE AND DIESEL ENGINE EXHAUST IN MICE

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TWO-YEAR CARCINOGENICITY NOSE-ONLY INHALATION STUDY OF ROOM AGED CIGARETTE SIDESTREAM SMOKE AND DIESEL ENGINE EXHAUST IN MICE

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SPONSOR:
Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

Protocol Date: _____

CONTRACT LABORATORY:
Battelle, Pacific Northwest Laboratories (BNW)
Life Sciences Laboratory (LSL-II Building)
P.O. Box 999
Richland, Washington 99352

Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

I. STUDY TITLE

Two-Year Carcinogenicity Nose-Only Inhalation Study of Room Aged Cigarette Sidestream Smoke and Diesel Engine Exhaust in Mice

II. PROJECT OBJECTIVE

The objective of this study is to determine the chronic carcinogenic potential of RASS administered by nose-only inhalation to male and female mice 6 hours daily, 5 days/week for two years. A diesel engine exhaust (DEE) exposure group will be included as a positive control. Non-neoplastic and neoplastic lesions particularly in the respiratory tract will be of major interest. Systemic effects (e.g., changes in body and organ weights, signs of intoxication) will also be determined. Effects will be compared to those seen in the sham-exposed (filtered air) negative and DEE-exposed positive control groups. Biomonitoring will be performed on RASS- and DEE-exposed rats.

III. STUDY SCHEDULE

A. Mice Arrive - week of

B. Start of exposure -

C. Last day of exposure -

IV. PROJECT NUMBER

V. PROTOCOL DATE

VI. SPONSOR

Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

VII. SPONSOR'S REPRESENTATIVE

George J. Patskan, PhD

VIII. TESTING FACILITY

Battelle, Pacific Northwest Laboratories (BNW)
Toxicology Department K4-10
P.O. Box 999
Richland, Washington 99352

IX. STUDY DIRECTOR AND PRINCIPAL INVESTIGATOR

Earl W. Morgan, DVM, ACVPM, DABT

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X. TEST ARTICLE DESCRIPTION

A. Identification

1. Room Aged Sidestream Smoke (RASS)

RASS will be obtained by aging sidestream smoke (SS) for 0.5 hours (mean age) in a room. SS will be generated from the standard reference filter cigarette, 1R4F, smoked in basic conformity with ISO standards 3402, 4387, and 3308 (1991). The cigarettes will be smoked by a 30-port smoking machine (CH Technologies, Westwood, NJ).

B. Lot Number

C. How Supplied

D. Storage Conditions

Cigarettes will be stored in a freezer at -16 ± 2°C. They will be preconditioned for at least 48 hours at room conditions (22 ± 2°C and 60 ± 10% RH) prior to smoking. Distribution and handling during the course of the study will be conducted in such a manner that proper identification will be maintained and contamination avoided.

E. Source

Philip Morris

XI. POSITIVE CONTROL DESCRIPTION

A. Diesel Engine Exhaust

The DEE will be generated from a light-duty pickup truck engine, mounted on a shock mount engine stand attached to a dynamometer system. The dynamometer will be programmed to simulate the EPA Urban Dynamometer Driving Schedule (40CFR Ch. 1, Pt. 86, App I).

B. Storage Condition

Diesel fuel will be stored in tank external to the building with a small day tank in the generator room.

C. Source

XII. TEST ATMOSPHERE

On-line monitoring of the mass concentration of RASS and DEE will be accomplished by two Tapered Element Oscillating Microbalance Mass Monitors (TEOM Model 1400, Rupprect & Patashnick Co., Inc., Albany, NY). The TOEMs will sample RASS and DEE aerosols from a representative exposure port in the exposure unit. Exposure concentrations will be controlled to within ±20 % of target concentration by adjustment of the exposure unit dilution airflow. Mass concentration will be monitored in one of each pair of exposure units at a time.

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A real time aerosol monitor (RAM; MIE, Inc., Bedford, MA) will be used to monitor the concentration of RASS as it enters the distribution line from the aging room. Aerosol concentrations will be monitored with the RAM twice per hour over the duration of the daily generation period. The relative response of the RAM to the aerosol concentration (volts per unit concentration) will be determined prior to the start of exposure. RAM response will be evaluated by comparing the measured RAM voltage to the aerosol concentration of RASS determined from independent filter samples.

The total particulate mass (TPM) of both RASS and DEE in the test atmosphere during the exposure will be determined from duplicate Cambridge filter samples from both the distribution line at the exit from the aging room and two exposure ports from each exposure unit collected over the duration of the generation period. These filters will be analyzed gravimetrically and/or by UV analysis. Filter sample extracts will be analyzed as soon as feasible following collection and preparation.

The buildup and decay of the test article concentration in the exposure unit will be determined prior to start of the study. The time to buildup to 90% of the target concentration (T_{90}) and the time to decay to 10% of the target concentration (T_{10}) will be determined.

The particle size distribution of the aerosol in the exposure unit will be measured prior to the start of exposure and once a month during the exposure phase. Median diameters and geometric standard deviations (GSD) will be reported.

Uniformity of the concentration and particle size distribution of the test article in the nose-only exposure unit will be determined during the prestart phase of the study. Uniformity of test article concentration will be demonstrated by monitoring one port on each level with the TEOM or RAM. Uniformity of particle size distribution will be demonstrated by samples taken at the top, middle and bottom levels of the exposure unit.

XIII. INHALATION EXPOSURE SYSTEM

A. Exposure Room

Rooms 523 and 531, LSL-II Building

B. Exposure Unit

Cannon flow-past nose-only exposure units. Each unit has 104 exposure ports, 90 of which will be used for rat exposures. The remaining ports will be used for sampling or closed off. Each exposure unit will be contained in a rigid clear plastic cabinet to assure no contamination of the room by the test article aerosol. Airflow through the hood will be maintained at approximately 15 cfm to assure proper cooling of the mice in the restraint tubes. The exposure unit can be rotated so that all mice may be easily observed during exposure.

C. Exposure Generator

RASS will be obtained by aging sidestream smoke (SS) for 0.5 hours (mean age) in a 30 m^3 room. SS will be generated from the standard reference filter cigarette, 1R4F, smoked by a 30-port smoking machine (CH Technologies, Westwood, NJ) in basic conformity with ISO standards 3402, 4387, and 3308 (1991). Mainstream smoke from the smoking machine will be routed through a filter system to remove the majority of the particulate material prior to being routed to the building exhaust. A stainless steel cone will be fitted over the smoking machine to extract the SS which will be mixed with conditioned dilution air (22 ± 2°C and 60 ± 10% RH) before being injected into a smoke aging room by a flow-controlled fan. The

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entire flow from the aging room will be delivered to the exposure rooms via a stainless steel delivery tube. The required flow of RASS will be siphoned from this delivery line by a pressurized-air-controlled ejector tube, mixed with conditioned air to achieve the proper concentration, and injected into the nose only exposure unit. Exhaust from the exposure units will be routed through a filter system to remove the majority of the particulate material prior to being routed to the building exhaust.

DEE will be generated from a light-duty pickup truck engine, mounted on a shock mount engine stand attached to a dynamometer system. The dynamometer will be programmed to simulate the EPA Urban Dynamometer Driving Schedule (40CFR Ch. 1, Pt. 86, App I). A constant flow of DEE from the engine will be delivered from a plenum downstream of the engine muffler to the exposure rooms through a heated stainless-steel deliver line. The required flow of DEE will be siphoned from this delivery line by a pressurized-air-controlled ejector tube, mixed with conditioned air to achieve the proper concentration, and injected into the nose only exposure unit. All DEE exhaust will be routed to the building exhaust.

XIV. TEST SYSTEM SPECIFICATIONS

Species:	Mus musculus
Strain:	TBD (VAF)
Source:	Charles River Laboratories Raleigh, NC
Age at Arrival:	4-5 weeks
Age at Study Start:	6-7 weeks
Total Number of Animals:	475 males; 475 females
Exposure Tube Acclimation Period:	~5 days
Identification:	Tail tattoo

XV. REASON FOR SELECTION

The ____ mouse was selected for this study on the basis of data available in the literature and a 13-week pilot study.

XVI. RANDOMIZATION

The mice which adapt to the exposure tubes will be randomly assigned to exposure groups by using body weight as a blocking variable to ensure that there are no statistically significant differences in initial group mean body weights. The weight distribution range (by sex) of the mice selected for the study will be as narrow as possible. A sufficient quantity of mice will be ordered and adapted to the exposure restraint tubes to ensure that no mouse will be selected whose body weight exceeds ±20% of the mean (by sex) at the start of the study. The Xybion Path/Tox System (Xybion Medical Systems Corporation, Cedar Knolls, NJ) will be used for randomization.

XVII. HOUSING AND MAINTENANCE

Mice shipping crates will be examined upon arrival for evidence of conditions likely to permit exposure to pathogens (soiled, wet, or otherwise damaged). The uncrating will be conducted at the door of the animal room. While being removed from the crates, the mice will be examined for evidence of shipping stress.

The mice will be acclimated in Room ____ of the LSL-II Building for 2 weeks prior to the start of exposure. Mice will remain on quarantine status until health screen procedures are completed, approximately 3 weeks after their arrival.

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Throughout the study, cage space will meet the requirements stated in the 85-23 (1985) NIH "Guide for Care and Use of Laboratory Animals". The BNW animal care and use program, including the facility used for this study, is accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

The mice will be housed approximately 5 mice per cage in hanging wire cages prior to identification and randomization at which time they will be housed individually in stainless steel wire cage units on stainless steel racks. Mice will be individually housed for the remainder of the study.

Room temperatures during the acclimatization and study will be maintained at 75 ± 2°F and relative humidities at 55 ± 15%. Measurements will be recorded at ~1 hour intervals.

Twelve hours light and twelve hours dark will be maintained with light starting at 0600.

Within 48 hours of arrival 5 mice/sex will be examined by gross necropsy, histopathology, and serological testing for evidence of disease and the presence of potentially pathogenic organisms. Sera will be tested for antibodies to Sendai virus, mouse hepatitis virus, GDVII virus, minute virus of mice, pneumonia virus of mice (PVM) and *Mycoplasma pulmonis*. Mice will be released for study if the health screen doesn't provide evidence of pathogens or disease. The clinical veterinarian will make a visual inspection of the mice to be used in the study just prior to their release for the study. Five mice per sex that were not used for the exposures will be reevaluated for evidence of disease 18-21 days after arrival at BNW.

Sentinel mice (15M,15F) will be selected from the extra mice prior to the start of exposures. Serological evaluations will be performed on 5/sex at 6, 12, and 18 months. Serological evaluations will be performed on 5/sex at the time of terminal sacrifice from the filtered air control group of mice.

During the acclimation period, approximately 7-10 days prior to the start of exposure, mice will be placed in nose-only exposure restraint tubes for increasing time up to 6 hours daily to allow them to adapt to confinement in the tubes. The mice which adapt to the restraint tubes will then be weighed, randomized, assigned to exposure concentration groups and identified individually with a unique number tail tattoo approximately two days before the exposure period.

Mice not used for the study will be euthanized by inhalation of 70% CO_2 one week after the start of the study. The disposition of these mice will be recorded on the Animal Disposition Record and retained in the study files.

Mice which die during the first week of the study will be replaced from the pool of unused mice.

XVIII. DIET AND WATER

NIH-07 Open Formula diet will be provided *ad libitum* except during the inhalation exposures when mice are in restraint tubes.

This diet is analyzed for contaminants and some nutrient components; these analyses are reviewed for acceptability using established standards prior to use of the food. There are no known contaminants in the diet which could be expected to alter the outcome of the study.

Fresh softened water (ion exchange softener, Illinois Water Treatment Company, Model 2R-2240, Rockford, IL) will be supplied *ad libitum* except during exposures. An automatic watering system (Edstrom Industries, Waterford, WI) will be used during the quarantine/acclimatization period and throughout the study. Water bottles will also be provided for the first three days after arrival.

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Representative samples of animal drinking water from the LSL-II facility will be analyzed for contaminants at least once per year. There are no known contaminants in the drinking water which could be expected to alter the outcome of the study. The hardness of the water will be checked approximately once every week. Records will be retained in the LSL-II Building Engineer's office.

XIX. ENVIRONMENTAL MONITORING

A. Air Supply

Room and exposure supply air will be HEPA-filtered. Both room and exposure exhaust air will pass through a series of two HEPA filters.

B. Temperatures

Temperatures in each exposure unit cabinet and in the exposure air stream at a nose port will be monitored at ~2-minute intervals and recorded at ~60 minute intervals during the daily exposure period. If the temperature is not within the acceptable range 75 ± 4°F, the system will alarm. Daily means for the exposure cabinet and the exposure atmosphere will be maintained within 75 ± 4°F.

Temperatures in the animal room will be monitored at ~2-minute intervals and recorded once every hour. If the temperature is not within the acceptable range 75 ± 2°F, the system will alarm. The acceptable range for individual animal room measurements and the daily mean will be 75 ± 2°F.

C. Relative Humidity

Relative humidity will be monitored at a nose-port in each exposure unit and recorded at ~60 minute intervals during the exposure period. If the relative humidity is not within the acceptable range 55 ± 15%, the system will alarm. Daily means for the exposure unit will be maintained within 55 ± 15%.

Animal room humidity will be monitored and recorded approximately once every hour. If the relative humidity is not within the acceptable range 55 ± 15%, the system will alarm. The acceptable daily mean is 55 ± 15% relative humidity.

D. Airflow

Airflow will be monitored at an inlet and exhaust orifices using a calibrated photohelic pressure gauge. Both flows will be recorded once per hour during the exposure period. The acceptable minimum inlet flow is 250 ml/min per occupied exposure port.

Measurements out of specified limits will be recorded and result in an alarm so that the operator can take appropriate actions.

XX. EFFLUENT TREATMENT

Exposure unit exhaust will be passed through a series of two HEPA filters and a catalytic converter to remove all test article. The concentration of test article in the building exhaust will be measured once during the study to determine the efficiency of the effluent treatment system.

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XXI. EXPERIMENTAL DESIGN

A. Route of Administration and Reason for Selection

The test articles will be administered by nose-only inhalation at concentrations of 1, 3 and 10 mg/m^3 of RASS and ____ mg/m3 of DEE. A filtered air control group will be included. The concentration of RASS and the route of administration used in this study were selected on the basis of route of human exposure and to provide target particle concentrations which exceed those determined for extreme human exposure to environmental tobacco smoke by a factor of approximately 10. The DEE concentrations were selected on the basis of data in the literature which indicate that this concentrations should result in a measurable carcinogenic response in the mouse and a comparable total particulate matter content to the RASS exposure.

B. Experimental Design

Group Number	Exposure Concentration (mg/m^3)	Core Study Mice	Lung Burden and Lung Clearance[a]	CoHb[b]	Total
1	0	60M	18M	12M	90M
		60F	18F	12F	90F
2	RASS (1)	60M	18M	12M	90M
		60F	18F	12F	90F
3	RASS (3)	60M	18M	12M	90M
		60F	18F	12F	90F
4	RASS (10)	60M	18M	12M	90M
		60F	18F	12F	90F
5	DEE (TBD)	60M	18M	12M	90M
		60F	18F	12F	90F
Sentinels[d]	0	15M	–	–	15M
		15F	–	–	15F

[a]Four mice/sex will be sacrificed at 4 timepoints. Two additional mice/sex/group are included to be used if needed.

[b]Five mice/sex will be bled at 6, 12, and 18 months. Mice will be allowed to survive at 6 and 12 months. Carboxyhemoglobin will also be determined from 5 mice/sex/group from the core study at terminal sacrifice.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

C. Animal Identification

Group Number	Exposure Concentration (mg/m^3)	Core Study Mice[a]	Lung Burden and Lung Clearance[a]	CoHb
1	0	1-60 (M) *101-120 (F)*	61-78 (M) *161-178 (F)*	79-90 (M) *179-190 (F)*
2	RASS (1)	201-220 (M) 301-320 (F)	261-278 (M) 361-378 (F)	279-290 (M) 379-390 (F)
3	RASS (3)	401-420 (M) 501-520 (F)	461-478 (M) 561-578 (F)	479-490 (M) 579-590 (F)
4	RASS (10)	601-620 (M) 701-720 (F)	661-678 (M) 761-778 (F)	679-690 (M) 779-790 (F)
5	DEE (TBD)	801-820 (M) 901-920 (F)	861-878 (M) 961-978 (F)	879-890 (M) 979-990 (F)
Sentinels	0	SM1-SM15 SF1-SF15	– –	– –

D. Route of Administration

Nose-only inhalation

E. Frequency/Duration

Six hours/day plus T_{90}; 5 days/week; up to 104 weeks; excluding weekends and holidays

F. Daily Observations

Twice daily for moribundity and mortality on all surviving mice.

G. Clinical Signs

Weekly for all surviving core study mice and prior to unscheduled sacrifice for moribund or humane sacrifice mice.

H. Body Weights

Weekly for the first 13 weeks, and at 4-week intervals thereafter (every 2 weeks during the last 13 weeks if needed)on all surviving core study mice.

I. Urine Nicotine/Cotinine

Six/sex, selected at random from the core study animals, from the RASS treated and filtered air control groups at 6, 12, 18, and 24 months. Mice will be placed in metabolism cages for a 16 hour urine collection.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

J. Carboxyhemoglobin

Five/sex/group from designated animals at 6, 12, and 18 months and 5/sex/group selected at random from the core study animals at terminal sacrifice. Mice will be removed from the exposure chamber within one hour before the end of the daily exposure period and bled from the supra-orbital sinus.

K. Clinical Pathology Evaluations

Fifteen mice/sex/group from the core study mice, prior to terminal sacrifice, will be anesthetized with ~70% CO_2 and blood samples will be collected from the retra-orbital sinus into tubes containing potassium EDTA for a complete blood count. At terminal necropsy the remaining mice and all moribund sacrifice mice will have a slide prepared for a differential leukocyte count. The slides will only be evaluated if abnormalties are detected in the CBCs.

L. Lung Clearance

During the 15th month 18 mice/sex/group will be exposed to 10 mg TiO_2/m^3 for 5 consecutive days. Lung burdens of TiO_2 will be determined, using ICP-AES techniques, on 4 animals/group at time points to be determined from the results of the clearance study conducted with the 13-week subchronic study.

M. Minute Volume

Respiratory physiology data will be collected, using plethysmographs, between 1 hour after the start of exposure and the end of the exposure period for 6 mice/sex/group selected at random from the core study animals.

Tidal volume (ml) and respiration rate (breaths/min) will be monitored continuously for 10 minutes. Average tidal volume and respiration rates will be calculated and stored for all breaths occurring during each 10-second interval of monitoring. Minute volume (ml/min) will be calculated as the product of the 10-second average tidal volume and the 10-second average respiration rate. The mean and standard deviation of the minute volume for the entire 10-minute recording session will then be calculated from the 10-second average minute volumes.

Body weights will be recorded on these mice on the day that the minute volume data are collected. If minute volume data are not collected on a scheduled weighing day, these weights will be in addition to the regular weekly body weights.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

XXII. POSTMORTEM OBSERVATIONS AND MEASUREMENTS

A. Necropsy

A complete necropsy will be performed on all core study mice found dead, moribund sacrificed or at terminal sacrifice. Findings will be recorded on an Individual Animal Necropsy Record (IANR) form. All surviving mice will be necropsied on the day following the last day of exposure. Mice will be killed by anesthetization with CO_2 followed by exsanguination. Necropsies will include an external examination of all body orifices, an examination of tissues/organs, and fixation in 10% neutral buffered formalin (NBF) of the following tissues:

Adrenals
Brain (medulla/pons, cerebellar cortex, cerebral cortex)
Ceacum
Colon
Duodenum
Esophagus
Eyes
Femur (including joint)
Gallbladder
Harderian glands
Heart/aorta
Ileum
Jejunum
Kidneys
Liver
Lungs (trachea, larynx, tongue, pharynx)
Lymph nodes
Mammary gland/skin
Nose
Oral Cavity
Ovaries
Pancreas
Pituitary
Preputial/clitoral glands
Prostate
Rectum
Salivary glands
Sciatic nerve
Seminal vesicles/coagulation glands
Spinal cord (cervical, thoracic, lumbar)
Spleen
Sternum with bone marrow
Stomach
Testes/epididymis
Thigh muscle
Thymus
Thyroid (including parathyroids)
Tissue masses/tumors
Urinary bladder
Uterus
Zymbal's gland

B. Organ Weights

Organ weights will be recorded from all core study mice for both adrenal glands (0.001 g), brain (0.01 g), epididymides (0.001 g), heart (0.01g), kidneys (0.01g), liver (0.01 g), lung with trachea (0.01 g), spleen (0.01 g), and testes (0.01 g). Organ to body weight and organ to brain weight ratios will be calculated. Organ weights from moribund/humane sacrifices will be collected and reported, but not included in the data analysis.

C. Histopathology

Organs/tissues collected from the filtered air control and the high concentration RASS and DEE groups will be processed to slides and stained with hematoxylin and eosin for histopathologic examination. Special stains will be used at the discretion of the pathologist. Data will be entered onto the Xybion Path/Tox System for all mice.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

A complete histopathologic evaluation inclusive of gross lesions will be performed on all core study mice from the filtered air control and the high concentration RASS and DEE groups sacrificed at the end of the exposure period. Histopathologic evaluation will be conducted on gross lesions and designated tissues from all core study animals. Tissues exhibiting effects in the high concentration group(s) will be examined in the lower concentration group(s) and in the animals sacrificed at the end of the recovery period to a no effect level. Slides may be peer reviewed by the Sponsor. A complete histopathologic evaluation will be conducted on the following tissues:

Accessory genital organs (prostate, seminal vesicles, coagulation glands)
Adrenals, right and left
Aorta (throacic)
Brain (cerebral cortex, cerebellar cortex, pons/ medulla oblongata)
Caecum
Clitoral glands
Colon
Duodenum
Epididymis
Eyes with optic nerve (if grossly abnormal)
Femur, including joint
Harderian glands
Heart
Ileum
Jejunum
Kidney, right and left
Larynx/laryngopharynx (step sections, 4 levels, laryngopharynx at the base of epiglottis)
Liver, gallbladder
Lungs (6-μm sections every 5 mm)
Lymph nodes (mandibular, mesenteric, bronchial and mediastinal)
Mammary glands
Musculature (thigh)
Nose/nasopharynx (4 levels; Young, 1981)
Oral cavity
Ovaries (mesovaries), right and left
Pancreas
Parathyroid glands
Peripheral nerve (sciatic)
Pituitary gland
Preputial glands
Rectum
Salivary glands (submandibular and sublingual)
Skin
Spinal cord (cervical, thoracic, and lumbar)
Spleen
Sternum with bone marrow
Stomach (forestomach and glandular stomach)
Testes, right and left
Thymus
Thyroid glands
Tongue
Trachea
Urinary bladder
Uterus
Zymbal's glands
All grossly visible tumors or lesions suspected being tumors

D. Statistical Analysis

Results from this study will include incidence tables of clinical signs, gross lesions, and histopathological observations. Group means will be calculated for:

Body weight
Body weight gain
Organ weight
Organ:body weight ratio
Organ:brain weight ratio
Leukocyte parameters
Nicotine and cotinine levels
Lung clearance

Any data set with a sample size less than six will have only means and standard deviations calculated. Group variances for body weight, clinical pathology and organ weight data will be compared using Bartlett's test. When the differences between group variances are not significant ($p>0.01$), a one-way analysis of variance (ANOVA) will be performed. If significant differences ($P<0.01$) among the means are indicated by the ANOVA, Dunnett's multiple comparison test will be used to determine the intergroup differences. Dunnett's

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

makes pairwise comparisons among all group means including the control groups. Significance will be declared at the 0.05 and 0.01 alpha levels.

In the event that Bartlett's test indicates significant differences between group variances for a given parameter, the mean values between the control and each concentration group will be compared using the Behrens-Fisher *t*-test (Satterthwaite's method will be used to adjust for degrees of freedom). Significance will be declared at the 0.05 and 0.01 alpha levels if the P value is less than alpha divided by the number of comparisons made (Bonferroni's adjustment for multiple comparisons; Miller 1981).

The percent difference in mean body weights (MBW) between treated and control animals will be calculated as follows:[1]

$$\frac{\text{MBW of Exposed Group - MBW of Control Group}}{\text{MBW of Control Group}} \times 100\%$$

E. Study Conduct and Records Retention

Documentation will be maintained in such a manner that confidentiality for the Sponsor, in all aspects of the study conduct, will be assured.

This protocol will be the controlling document. The Study Director is to be notified immediately for clarification if discrepancies occur between the protocol and the SOPs.

Any changes to this protocol will be made in the following manner. If BNW initiates the change, not associated with cost, verbal (telephonic) approval will be obtained from the Sponsor followed by written documentation by BNW to the Sponsor. Any change which impacts the cost or schedule of the study will be documented in writing and approved by the Sponsor Representative's signature prior to implementation. The Sponsor may initiate modification to the protocol by telephonic authorization to BNW followed by written documentation as stated above.

This study will be conducted in compliance with Good Laboratory Practice regulations, 21 CFR 58. All records required to reconstruct the study will be maintained as stipulated in 21 CFR 58.190. All paraffin blocks and wet tissues resulting from any portion of this study will be retained by BNW until 6 months after acceptance of the final report at which time they will be sent to the Sponsor. If requested by the sponsor, all microscopic slides will be submitted to the Sponsor with the final draft report.

Records to be retained in study archives will be specified by the SOP entitled "Records to be Retained for Philip Morris Studies". Records that accumulate during the study will be retained at BNW until they are shipped to the Sponsor immediately prior to the termination of the contract or until the Sponsor requests transfer, whichever occurs first.

F. Report

Following a Quality Assurance audit of the raw data and data tables, a complete and detailed draft report will be submitted to the Sponsor within the time frame of the contract.

G. References

Miller, R.G. Jr. 1981. *Simultaneous Statistical Inference*. Springer-Verlag, New York, NY.

[1]This procedure is currently in use by the National Toxicology Program, NIEHS, Research Triangle Park, NC.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

XXIII. BNW APPROVAL

Earl W. Morgan, DVM, ACVPM, DABT
Principal Investigator

Date

R.A. Gelman, MS
Quality Assurance Auditor

Date

XXIV. SPONSOR APPROVAL

George J. Patskan, PhD
Study Monitor

Date

Sponsor's Representative

Date

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THIRTEEN-WEEK NOSE-ONLY INHALATION PILOT STUDY IN MICE

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THIRTEEN-WEEK NOSE-ONLY INHALATION PILOT STUDY IN MICE

SPONSOR:
Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

Protocol Date: _____

CONTRACT LABORATORY:
Battelle, Pacific Northwest Laboratories (BNW)
Life Sciences Laboratory (LSL-II Building)
P.O. Box 999
Richland, Washington 99352

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

I. STUDY TITLE

Thirteen-Week Nose-Only Inhalation Pilot Study in Mice

II. PROJECT OBJECTIVE

The objective of this study is to determine the adaptability of C57BL/6 mice to the stress of a 6 hour per day, 5 days per week, nose-only inhalation exposure for thirteen weeks. The C57BL/6 mouse is the preferred strain for a two-year carcinogenicity bioassay to be conducted on the carcinogenic potential of RASS in mice. The study will include B6C3F1 and CD-1 mice for comparison. Results of this study will be used to select the strain of mice to be used for a two-year carcinogenicity bioassay of RASS and DEE in mice.

III. STUDY SCHEDULE

A. Arrival - week of

B. Start of exposure -

C. Last day of exposure -

IV. PROJECT NUMBER

V. PROTOCOL DATE

VI. SPONSOR

Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

VII. REPRESENTATIVE

George J. Patskan, PhD

VIII. TESTING FACILITY

Battelle, Pacific Northwest Laboratories (BNW)
Toxicology Department K4-10
P.O. Box 999
Richland, Washington 99352

IX. STUDY DIRECTOR AND PRINCIPAL INVESTIGATOR

Earl W. Morgan, DVM, ACVPM, DABT

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X. INHALATION EXPOSURE SYSTEM

A. Exposure Room

Room ____, LSL-II Building

1. Exposure Unit

Cannon flow-past nose-only exposure units. Each unit has 104 exposure ports, 90 of which will be used for rat exposures. The remaining ports will be used for sampling or closed off. The exposure unit is traditionally contained in a rigid, clean plastic cabinet to avoid contamination of the room by the test article aerosol. The sample system will be used in this case, although the test article is filtered air. Airflow through the hood will be maintained at approximately 15 cfm to assure proper cooling of the mice in the restraint tubes. The exposure unit can be rotated so that all mice may be easily observed during exposure.

XI. TEST SYSTEM

A. Specifications

Species:	Mus musculus
Strain:	C57BL/6 (VAF) B6C3F1 (VAF) CD-1 (VAF)
Source:	Charles River Laboratories Raleigh, NC
Age at Arrival:	4-5 weeks
Age at Study Start:	6-7 weeks
Total Number of Animals:	45 males; 45 females
Exposure Tube Acclimation Period:	7-10 days
Identification:	Tail tattoo

B. Reason for Selection

The C57BL/6 (VAF) mouse was selected for a 2-year carcinogenicity bioassay in mice of RASS in mice on the basis of data available in the literature in which this is the only strain of mice in which carcinogenisis has been reported for both RASS and DEE. The B6C3F1 (VAF) and CD-1 (VAF) are being included for comparative purposes and evaluation as possible alternatives in the event that the C57BL/6 dose not adapt to the nose-only restraint tubes for prolonged periods of time.

C. Randomization

The mice which adapt to the exposure tubes will be randomly assigned to exposure groups by using body weight as a blocking variable to ensure that there are no statistically significant differences in initial group mean body weights. The weight distribution range (by sex) of the mice selected for the study will be as narrow as possible. A sufficient quantity of mice will be ordered and adapted to the exposure restraint tubes to ensure that no rat will be selected whose body weight exceeds ±20% of the mean (by sex) at the start of the study. The XYBION PATH/TOX System (XYBION Medical Systems Corporation, Cedar Knolls, NJ) will be used for randomization.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

D. Housing and Maintenance

Mice shipping crates will be examined upon arrival for evidence of conditions likely to permit exposure to pathogens (soiled, wet, or otherwise damaged). The uncrating will be conducted at the door of the animal room. While being removed from the crates, the mice will be examined for evidence of shipping stress.

The mice will be acclimated in room ---- of the LSL-II Building for 10-14 days prior to the start of exposure. Mice will remain on quarantine status until health screen procedures are completed, approximately 3 weeks after their arrival.

Throughout the study, cage space will meet the requirements stated in the 85-23 (1985) NIH "Guide for Care and Use of Laboratory Animals". The BNW animal care and use program, including the facility used for this study, is accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

The mice will be housed approximately 5 mice per cage in hanging wire cages prior to identification and randomization at which time they will be housed individually in stainless steel wire cage units on stainless steel racks. Mice will be individually housed for the remainder of the study.

Room temperatures during the acclimatization and study will be maintained at 75 ± 2°F and relative humidities at 55 ± 15%. Measurements will be recorded at ~1 hour intervals.

Twelve hours light and twelve hours dark will be maintained with light starting at 0600.

The clinical veterinarian will make a visual inspection of the mice to be used in the study just prior to their release for the study. Five mice per sex that were not used for the exposures will be evaluated for evidence of disease 18-21 days after arrival at BNW. Gross necropsy, histopathology, and serological testing for evidence of disease and the presence of potentially pathogenic organisms will be performed. Sera will be tested for antibodies to Sendai virus, mouse hepatitis virus, GDVII virus, minute virus of mice, pneumonia virus of mice (PVM) and Mycoplasma pulmonis. Mice will be released from quarantine if the health screen doesn't provide evidence of pathogens or disease.

Serological evaluations will be performed on 5 mice/sex at the time of terminal sacrifice.

During the acclimation period, approximately 7-10 days prior to the start of exposure, mice will be placed in nose-only exposure restraint tubes for increasing time up to 6 hours daily for five days to allow them to adapt to confinement in the tubes. The mice which adapt to the restraint tubes will then be weighed, randomized, assigned to exposure concentration groups and identified individually with a unique number tail tattoo approximately two days before the exposure period.

Mice not used for the study will be euthanized one week after the start of the study. The disp osition of these mice will be recorded on the Animal Disposition Record and retained in the study files.

Mice which die during the first week of the study will be replaced from the pool of unused mice.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

E. Diet and Water

NIH-07 Open Formula diet will be provided *ad libitum* except during the inhalation exposures when mice are in restraint tubes.

This diet is analyzed for contaminants and some nutrient components; these analyses are reviewed for acceptability using established standards prior to use of the food. There are no known contaminants in the diet which could be expected to alter the outcome of the study.

Fresh softened water (Ion exchange softener, Illinois Water Treatment Company, Model 2R-2240, Rockford, IL) will be supplied ad libitum except during exposures. An automatic watering system (Edstrom Industries, Waterford, WI) will be used during the quarantine/acclimatization period and throughout the study. Water bottles will also be provided for the first three days after arrival.

Representative samples of animal drinking water from the LSL-II facility will be analyzed for contaminants at least once per year. There are no known contaminants in the drinking water which could be expected to alter the outcome of the study. The hardness of the water will be checked approximately once every week. Records will be retained in the LSL-II Building Engineer's office.

F. Environmental Monitoring

1. Air Supply

Room and exposure supply air will be HEPA-filtered. Both room and exposure exhaust air will pass through a series of two HEPA filters.

2. Temperatures

Temperatures in each exposure unit cabinet and in the exposure air stream at a nose port will be monitored at ~2-minute intervals and recorded at ~60 minute intervals during the daily exposure period. If the temperature is not within the acceptable range 75 ± 4°F, the system will alarm. Daily means for the exposure cabinet and the exposure atmosphere will be maintained within 75 ± 4°F.

Temperatures in the animal room will be monitored at ~2-minute intervals and recorded once every hour. If the temperature is not within the acceptable range 75 ± 2°F, the system will alarm. The acceptable range for individual animal room measurements and the daily mean will be 75 ± 2°F.

3. Relative Humidity

Relative humidity will be monitored at a nose-port in each exposure unit and recorded at ~60 minute intervals during the exposure period. If the relative humidity is not within the acceptable range 55 ± 15%, the system will alarm. Daily means for the exposure unit will be maintained within 55 ± 15%.

Animal room humidity will be monitored and recorded once every hour. If the relative humidity is not within the acceptable range 55 ± 15%, the system will alarm. The acceptable daily mean is 55 ± 15% relative humidity.

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4. Airflow

Airflow will be monitored at an inlet orifice using a calibrated photohelic pressure gauge. Flow will be recorded once per hour during the exposure period. The acceptable minimum flow is 250 ml/min per occupied exposure port.

Measurements out of specified limits will be recorded and result in an alarm so that the operator can take appropriate actions.

XII. EXPERIMENTAL DESIGN

A. Route of Administration and Reason for Selection

For the planned two-year carcinogenicity bioassay the test articles will be administered by nose-only inhalation. The concentration of RASS and the route of administration were selected on the basis of route of human exposure. This study is designed to evaluate the ability of the selected strains of mice to adapt to the stress of confinement in the nose-only exposure tubes for 6 hours per day, 5 days per week (excluding holidays) for 13 weeks.

B. Experimental Design

Treatment	Number of Strains	Number of Mice/Strain	Daily Observations[a]	Clinical Signs[a]	Body Weights[b]	Total
Filtered Air	3	15M	15M	15M	15M	45M
	3	15F	15F	15F	15F	45F

[a]All survivors to that study day (twice daily for moribundity, mortality, and clinical signs)
[b]All survivors to scheduled weighing day

C. Animal Identification

Strain	Study Mice[a]
C57BL/6	1-15 (M) 101-115 (F)
B6C3F1	201-215 (M) 301-315 (F)
CD-1	401-415 (M) 501-515 (F)

1. Route of Administration

Nose-only inhalation

2. Frequency/Duration

Six hour/day; 5 days/week; at least 13 weeks, excluding holidays and weekends

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

3. Daily Observations

Twice daily for moribundity and mortality on all surviving mice.

4. Body Weights

Weekly on all surviving mice.

5. Clinical Signs

Weekly for all survivors and prior to unscheduled sacrifice for moribund or humane sacrifice mice.

D. Postmortem Observations and Measurements

1. Necropsy

A complete necropsy will be performed only on mice sacrificed as moribund or at termination of the study on mice exhibiting gross signs of stress. Findings will be recorded on an Individual Animal Necropsy Record (IANR) form. Mice, as needed, will be necropsied on the day following the last day of exposure. Mice will be killed by anesthetization with CO_2 followed by exsanguination. Necropsies will include an external examination of all body orifices, an examination of tissues/organs, and fixation in 10% neutral buffered formalin (NBF) only on tissues exhibiting gross abnormalities potentially related to stress.

2. Organ Weights

Testicular weight (0.01 g) will be recorded on all males. Additional organ weights will only be recorded from organs exhibiting gross signs.

3. Histopathology

Will only be performed at the discretion of the pathologist to evaluate the potential effects of stress. Data will be entered onto the Xybion Path/Tox System.

E. Statistical Analysis

Results from this study will include incidence tables of clinical signs, gross lesions and histopathological observations, if performed.

Group means will be calculated for:

Body weight
Body weight gain
Testicular weight

Any group with a sample size less than six will have only means and standard deviations calculated. Group variances for body weight and testicular weight data will be compared using Bartlett's test. When the differences between group variances are not significant ($p>0.01$), a one-way analysis of variance (ANOVA) will be performed. If significant differences ($P<0.01$) among the means are indicated by the ANOVA, Dunnett's multiple comparison test will be used to determine the intergroup differences. Dunnett's makes pairwise comparisons among all group means including the control groups. Significance will be declared at the 0.05 and 0.01 alpha levels.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

In the event that Bartlett's test indicates significant differences between group variances for a given parameter, the mean values between the control and each concentration group will be compared using the Behrens-Fisher *t*-test (Satterthwaite's method will be used to adjust for degrees of freedom). Significance will be declared at the 0.05 and 0.01 alpha levels if the P value is less than alpha divided by the number of comparisons made (Bonferroni's adjustment for multiple comparisons; Miller 1981).

The percent difference in mean body weights (MBW) between treated and control animals will be calculated as follows:[1]

$$\frac{\text{MBW of Exposed Group - MBW of Control Group}}{\text{MBW of Control Group}} \times 100\%$$

F. Study Conduct and Records Retention

Documentation will be maintained in such a manner that confidentiality for the Sponsor, in all aspects of the study conduct, will be assured.

This protocol will be the controlling document. The Study Director is to be notified immediately for clarification if discrepancies occur between the protocol and the SOPs. Any changes to this protocol will be made in the following manner. If BNW initiates the change, not associated with cost, verbal (telephonic) approval will be obtained from the Sponsor followed by written documentation by BNW to the Sponsor. Any change which impacts the cost or schedule of the study will be documented in writing and approved by the Sponsor Representative's signature prior to implementation. The Sponsor may initiate modification to the protocol by telephonic authorization to BNW followed by written documentation as stated above.

This study will be conducted in compliance with Good Laboratory Practice regulations, 21 CFR 58. All records required to reconstruct the study will be maintained as stipulated in 21 CFR 58.190. All paraffin blocks and wet tissues resulting from any portion of this study will be retained by BNW until 6 months after acceptance of the final report at which time they will be sent to the Sponsor. If requested by the sponsor, all microscopic slides will be submitted to the Sponsor with the final draft report.

Records to be retained in study archives will be specified by the SOP entitled "Records to be Retained for Philip Morris Studies". Records that accumulate during the study will be retained at BNW until they are shipped to the Sponsor immediately prior to the termination of the contract or until the Sponsor requests transfer, whichever occurs first.

G. Report

Following a Quality Assurance audit of the raw data and data tables, the results of this study will be included in the phase one report.

H. References

Miller, R.G. Jr. 1981. Simultaneous Statistical Inference. Springer-Verlag, New York, NY.

[1]This procedure is currently in use by the National Toxicology Program, NIEHS, Research Triangle Park, NC.

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

XIII. BNW APPROVAL

Earl W. Morgan, DVM, ACVPM, DABT
Principal Investigator

Date

R.A. Gelman, MS
Quality Assurance Auditor

Date

XIV. SPONSOR APPROVAL

George J. Patskan, PhD
Sponsor's Representative

Date

2029227900

Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

THIRTEEN-WEEK NOSE-ONLY INHALATION TOXICITY STUDY OF ROOM AGED CIGARETTE SIDESTREAM SMOKE AND DIESEL ENGINE EXHAUST IN MICE

"Use or disclosure of proposal data is subject to the restriction on the Title page of this Proposal."

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

THIRTEEN-WEEK NOSE-ONLY INHALATION TOXICITY STUDY OF ROOM AGED CIGARETTE SIDESTREAM SMOKE AND DIESEL ENGINE EXHAUST IN MICE

SPONSOR:
Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

CONTRACT LABORATORY:
Battelle, Pacific Northwest Laboratories (BNW)
Life Sciences Laboratory (LSL-II Building)
P.O. Box 999
Richland, Washington 99352

Protocol Date: _____

2029227902

Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

I. STUDY TITLE

Thirteen-Week Nose-Only Inhalation Toxicity Study of Room Aged Cigarette Sidestream Smoke and Diesel Engine Exhaust in Mice

II. PROJECT OBJECTIVE

Objectives of this study are to determine the toxicity of RASS and DEE administered by nose-only inhalation to male and female mice 6 hours per day, 5 days per week, for thirteen weeks to evaluate the system, to work out technical difficulties, and to establish laboratory procedures. The study will include groups of mice to be used for studies of potential carcinogenicity mechanisms. The study will also provide data on an additional group which will be allowed to recover for 13 weeks. Results of this study will be used to validate the doses of RASS for a 2-year carcinogenicity bioassay in mice and to select the dose of DEE to be used as the positive control in that study.

III. STUDY SCHEDULE

A. Arrival - week of

B. Start of exposure -

C. Last day of exposure -

IV. PROJECT NUMBER

V. PROTOCOL DATE

VI. SPONSOR

Philip Morris
Research Center
P.O. Box 26583
Richmond, Virginia 23261

VII. SPONSOR'S REPRESENTATIVE

George J. Patskan, PhD

VIII. TESTING FACILITY

Battelle, Pacific Northwest Laboratories (BNW)
Toxicology Department K4-10
P.O. Box 999
Richland, Washington 99352

IX. STUDY DIRECTOR AND PRINCIPAL INVESTIGATOR

Earl W. Morgan, DVM, ACVPM, DABT

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Source: https://www.industrydocuments.ucsf.edu/docs/zyxl0000

X. TEST ARTICLE DESCRIPTION

A. Identification

1. Room Aged Sidestream Smoke (RASS)

RASS will be obtained by aging sidestream smoke (SS) for 0.5 hours (mean age) in a room. SS will be generated from the standard reference filter cigarette, 1R4F, smoked in basic conformity with ISO standards 3402, 4387, and 3308 (1991). The cigarettes will be smoked by a 30-port smoking machine (CH Technologies, Westwood, NJ).

B. Lot Number

C. How Supplied

D. Storage Conditions

Cigarettes will be stored in a freezer at -16 ± 2°C. They will be preconditioned for at least 48 hours at room conditions (22 ± 2°C and 60 ± 10% RH) prior to smoking. Distribution and handling during the course of the study will be conducted in such a manner that proper identification will be maintained and contamination avoided.

E. Source

Philip Morris

XI. POSITIVE CONTROL DESCRIPTION

A. Diesel Engine Exhaust

The DEE will be generated from a light-duty pickup truck engine, mounted on a shock mount engine stand attached to a dynamometer system. The dynamometer will be programmed to simulate the EPA Urban Dynamometer Driving Schedule (40CFR Ch. 1, Pt. 86, App I).

B. Storage Condition

Diesel fuel will be stored in tank external to the building with a small day tank in the generator room.

C. Source

XII. TEST ATMOSPHERE

On-line monitoring of the mass concentration of RASS and DEE will be accomplished by two Tapered Element Oscillating Microbalance Mass Monitors (TEOM 1400, Rupprect & Patashnick Co., Inc., Albany, NY). The TOEMs will sample RASS and DEE aerosols from a representative exposure port in the exposure unit. Exposure concentrations will be controlled to within ±20 % of target concentration by adjustment of the exposure unit dilution airflow.

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A real time aerosol monitor (RAM; MIE, Inc., Bedford, MA) will be used to monitor the concentration of RASS as it enters the distribution line from the aging room. Aerosol concentrations will be monitored with the RAM twice per hour over the duration of the daily generation period. The relative response of the RAM to the aerosol concentration (volts per unit concentration) will be determined prior to the start of exposure. RAM response will be evaluated by comparing the measured RAM voltage to the aerosol concentration of RASS determined from independent filter samples.

The total particulate mass (TPM) of both RASS and DEE in the test atmosphere during the exposure will be determined from duplicate Cambridge filter samples from both the distribution line at the exit from the aging room and two exposure ports from each exposure unit collected over the duration of the generation period. These filters will be analyzed gravimetrically and/or by UV analysis. Filter sample extracts will be analyzed as soon as feasible following collection and preparation.

The buildup and decay of the test article concentration in the exposure unit will be determined prior to start of the study. The time to buildup to 90% of the target concentration (T_{90}) and the time to decay to 10% of the target concentration (T_{10}) will be determined.

The particle size distribution of the aerosol in the exposure unit will be measured prior to the start of exposure and once a month during the exposure phase. Median diameters and geometric standard deviations (GSD) will be reported.

Uniformity of the concentration and particle size distribution of the test article in the nose-only exposure unit will be determined during the prestart phase of the study. Uniformity of test article concentration will be demonstrated by monitoring one port on each level with the TEOM or RAM. Uniformity of particle size distribution will be demonstrated by samples taken at the top, middle and bottom levels of the exposure unit.

XIII. INHALATION EXPOSURE SYSTEM

A. Exposure Room

Rooms 523 and 531, LSL-II Building

B. Exposure Unit

Cannon flow-past nose-only exposure units. Each unit has 104 exposure ports, 90 of which will be used for rat exposures. The remaining ports will be used for sampling or closed off. Each exposure unit will be contained in a rigid clear plastic cabinet to assure no contamination of the room by the test article aerosol. Airflow through the hood will be maintained at approximately 15 cfm to assure proper cooling of the mice in the restraint tubes. The exposure unit can be rotated so that all mice may be easily observed during exposure.

C. Exposure Generator

RASS will be obtained by aging sidestream smoke (SS) for 0.5 hours (mean age) in a 30 m^3 room. SS will be generated from the standard reference filter cigar ette, 1R4F, smoked by a 30-port smoking machine (CH Technologies, Westwood, NJ) in basic conformity with ISO standards 3402, 4387, and 3308 (1991). Mainstream smoke from the smoking machine will be routed through a filter system to remove the majority of the particulate material prior to being routed to the building exhaust. A stainless steel cone will be fitted over the smoking machine to extract the SS which will be mixed with conditioned dilution air (22 ± 2°C and 60 ± 10% RH) before being injected into a smoke aging room by a flow-controlled fan. The

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entire flow from the aging room will be delivered to the exposure rooms via a stainless steel delivery tube. The required flow of RASS will be siphoned from this delivery line by a pressurized-air-controlled ejector tube, mixed with conditioned air to achieve the proper concentration, and injected into the nose only exposure unit. Exhaust from the exposure units will be routed through a filter system to remove the majority of the particulate material prior to being routed to the building exhaust.

DEE will be generated from a light-duty pickup truck engine, mounted on a shock mount engine stand attached to a dynamometer system. The dynamometer will be programmed to simulate the EPA Urban Dynamometer Driving Schedule (40CFR Ch. 1, Pt. 86, App I). A constant flow of DEE from the engine will be delivered from a plenum downstream of the engine muffler to the exposure rooms through a heated stainless-steel deliver line. The required flow of DEE will be siphoned from this delivery line by a pressurized-air-controlled ejector tube, mixed with conditioned air to achieve the proper concentration, and injected into the nose only exposure unit. All DEE exhaust will be routed to the building exhaust.

XIV. TEST SYSTEM SPECIFICATIONS

Species:	Mus musculus
Strain:	TBD (VAF)
Source:	Charles River Laboratories Raleigh, NC
Age at Arrive:	4-5 weeks
Age at Study Start:	6-7 weeks
Total Number of Animals:	275 males; 185 females (includes 55M/55F Big Blue mice)
Exposure Tube Acclimation Period:	~5 days
Identification:	Tail tattoo

XV. REASON FOR SELECTION

The ____ mouse was selected for this study on the basis of data available in the literature and a 13-week pilot study.

XVI. RANDOMIZATION

The mice which adapt to the exposure tubes will be randomly assigned to exposure groups by using body weight as a blocking variable to ensure that there are no statistically significant differences in initial group mean body weights. The weight distribution range (by sex) of the mice selected for the study will be as narrow as possible. A sufficient quantity of mice will be ordered and adapted to the exposure restraint tubes to ensure that no mouse will be selected whose body weight exceeds ±20% of the mean (by sex) at the start of the study. The Xybion Path/Tox System (Xybion Medical Systems Corporation, Cedar Knolls, NJ) will be used for randomization.

XVII. HOUSING AND MAINTENANCE

Mice shipping crates will be examined upon arrival for evidence of conditions likely to permit exposure to pathogens (soiled, wet, or otherwise damaged). The uncrating will be conducted at the door of the animal room. While being removed from the crates, the mice will be examined for evidence of shipping stress.

The mice will be acclimated in Room ____ of the LSL-II Building for 2 weeks prior to the start of exposure. Mice will remain on quarantine status until health screen procedures are completed, approximately 3 weeks after their arrival.

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Throughout the study, cage space will meet the requirements stated in the 85-23 (1985) NIH "Guide for Care and Use of Laboratory Animals". The BNW animal care and use program, including the facility used for this study, is accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

The mice will be housed approximately 5 mice per cage in hanging wire cages prior to identification and randomization at which time they will be housed individually in stainless steel wire cage units on stainless steel racks. Mice will be individually housed for the remainder of the study.

Room temperatures during the acclimatization and study will be maintained at 75 ± 2°F and relative humidities at 55 ± 15%. Measurements will be recorded at ~1 hour intervals.

Twelve hours light and twelve hours dark will be maintained with light starting at 0600.

The clinical veterinarian will make a visual inspection of the mice to be used in the study just prior to their release for the study. Mice will be released for study if the health screen doesn't provide evidence of pathogens or disease. Five mice per sex that were not used for the exposures will be reevaluated for evidence of disease 18-21 days after arrival at BNW. Sera will be tested for antibodies to Sendai virus, mouse hepatitis virus, GDVII virus, minute virus of mice, pneumonia virus of mice (PVM) and *Mycoplasma pulmonis*.

Sentinel mice (5M,5F) will be selected from the extra mice prior to the start of exposures. Serological evaluations will be performed on these mice at the time of terminal sacrifice of the core study mice.

During the acclimation period, approximately 7-10 days prior to the start of exposure, mice will be placed in nose-only exposure restraint tubes for increasing time up to 6 hours daily to allow them to adapt to confinement in the tubes. The mice which adapt to the restraint tubes will then be weighed, randomized, assigned to exposure concentration groups and identified individually with a unique number tail tattoo approximately two days before the exposure period.

Mice not used for the study will be euthanized one week after the start of the study. The disposition of these mice will be recorded on the Animal Disposition Record and retained in the study files.

Mice which die during the first week of the study will be replaced from the pool of unused mice.

XVIII. DIET AND WATER

NIH-07 Open Formula diet will be provided *ad libitum* except during the inhalation exposures when mice are in restraint tubes.

This diet is analyzed for contaminants and some nutrient components; these analyses are reviewed for acceptability using established standards prior to use of the food. There are no known contaminants in the diet which could be expected to alter the outcome of the study.

Fresh softened water (ion exchange softener, Illinois Water Treatment Company, Model 2R-2240, Rockford, IL) will be supplied *ad libitum* except during exposures. An automatic watering system (Edstrom Industries, Waterford, WI) will be used during the quarantine/acclimatization period and throughout the study. Water bottles will also be provided for the first three days after arrival.

Representative samples of animal drinking water from the LSL-II facility will be analyzed for contaminants at least once per year. There are no known contaminants in the drinking water which

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could be expected to alter the outcome of the study. The hardness of the water will be checked approximately once every week. Records will be retained in the LSL-II Building Engineer's office.

XIX. ENVIRONMENTAL MONITORING

A. Air Supply

Room and exposure supply air will be HEPA-filtered. Both room and exposure exhaust air will pass through a series of two HEPA filters.

B. Temperatures

Temperatures in each exposure unit cabinet and in the exposure air stream at a nose port will be monitored at ~2-minute intervals and recorded at ~60 minute intervals during the daily exposure period. If the temperature is not within the acceptable range 75 ± 4°F, the system will alarm. Daily means for the exposure cabinet and the exposure atmosphere will be maintained within 75 ± 4°F.

Temperatures in the animal room will be monitored at ~2-minute intervals and recorded once every hour. If the temperature is not within the acceptable range 75 ± 4°F, the system will alarm. The acceptable range for individual animal room measurements and the daily mean will be 75 ± 4°F.

C. Relative Humidity

Relative humidity will be monitored at a nose-port in each exposure unit and recorded at ~60 minute intervals during the exposure period. If the relative humidity is not within the acceptable range 55±15%, the system will alarm. Daily means for the exposure unit will be maintained within 55±15%.

Animal room humidity will be monitored and recorded once every hour. If the relative humidity is not within the acceptable range 55±15%, the system will alarm. The acceptable daily mean is 55±15% relative humidity.

D. Airflow

Airflow will be monitored at an inlet and exhaust orifices using a calibrated photohelic pressure gauge. Both flows will be recorded once per hour during the exposure period. The acceptable minimum inlet flow is 250 ml/min per occupied exposure port.

Measurements out of specified limits will be recorded and result in an alarm so that the operator can take appropriate actions.

XX. EFFLUENT TREATMENT

Exposure unit exhaust will be passed through a series of two HEPA filters and a catalytic converter to remove all test article. The concentration of test article in the building exhaust will be measured once during the study to determine the efficiency of the effluent treatment system.

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XXI. EXPERIMENTAL DESIGN

A. Route of Administration and Reason for Selection

The test articles will be administered by nose-only inhalation at concentrations of 1 and 10 mg/m^3 of RASS and 3 and 10 mg/m^3 of DEE. A filtered air control group will be included. The concentration of RASS and the route of administration used in this study were selected on the basis of route of human exposure and to provide target particle concentrations which exceed those determined for extreme human exposure to environmental tobacco smoke by a factor of approximately 10. The DEE concentrations were selected on the basis of data in the literature which indicate that these concentrations should result in a measurable carcinogenic response in the mouse.

B. Experimental Design

Group Number	Exposure Concentration (mg/m^3)	Core Study Mice[a,b,c]	Blue Mouse Micronucleus Assay Mice	Enzyme Assay Mice	Adducts Assay Mice	Plumonary Clearance Mice	Total
1	0	15M 15F	10M 10F	6M 6F	5M 5F	18M	54M 36F
2	1 (RASS)	15M 15F	10M 10F	6M 6F	5M 5F	18M	54M 36F
3	10 (RASS)	15M 15F	10M 10F	6M 6F	5M 5F	18M	54M 36F
4	3 (DEE)	15M 15F	10M 10F	6M 6F	5M 5F	18M	54M 36F
5	10 (DEE)	15M 15F	10M 10F	6M 6F	5M 5F	18M	54M 36F
Sentinels	0	5M 5F	– –	– –	5M 5F	– –	5M 5F

[a]Includes 5 mice which will be used for a 13 week recovery period.
[b]Blood will be collected from 5/sex/group for carboxyhemoglobin determination.
[c]Urine will be collected from 5/sex from controls and RASS treated mice for nicotine and cotinine determination.

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C. Animal Identification

Group Number	Exposure Concentration (mg/m^3)	Core Study Mice	Blue Mouse Micronucleus Assay Mice	Enzyme Assay Mice	Adducts Assay Mice	Plumonary Clearance Mice
1	0	1-15 (M) 101-115 (F)	16-25 (M) 116-125 (F)	26-31 (M) 26-31 (F)	32-36 (M) 32-36 (F)	37-54 (M) 137-154 (F)
2	1 (RASS)	201-215 (M) 301-315 (F)	216-225 (M) 316-325 (F)	226-231 (M) 326-331 (F)	232-236 (M) 332-336 (F)	237-254 (M) 337-354 (F)
3	10 (RASS)	401-415 (M) 501-515 (F)	416-425 (M) 516-525 (F)	426-431 (M) 526-531 (F)	432-436 (M) 532-536 (F)	437-454 (M) 537-554 (F)
4	3 (DEE)	601-615 (M) 701-715 (F)	616-625 (M) 716-725 (F)	626-631 (M) 726-731 (F)	632-636 (M) 732-736 (F)	637-654 (M) 737-754 (F)
5	10 (DEE)	801-815 (M) 901-915 (F)	816-825 (M) 916-925 (F)	826-831 (M) 926-931 (F)	832-836 (M) 932-936 (F)	837-854 (M) 937-954 (F)
Sentinels	0	SM1-SM5 SF1-SF5	– –	– –	– –	– –

D. Route of Administration

Nose-only inhalation

E. Frequency/Duration

Six hours/day plus T_{90}; 5 days/week; at least 13 weeks, excluding holidays and weekends

F. Daily Observations

Twice daily for moribundity and mortality on all surviving mice.

G. Clinical Signs

Weekly for all survivors and prior to unscheduled sacrifice for moribund or humane sacrifice mice.

H. Body Weights

Weekly on all surviving mice.

I. Urine Nicotine/Continine

During week 4 for 5/sex/RASS treated and filtered air control groups selected at random from the core study animals. Mice will be placed in metabolism cages for a 16 hour urine collection.

J. Micronucleus and Big Blue™ Mouse Assay

During week 5, the 10 Big Blue mice/sex/group will be anesthetized and the lungs perfused and removed aseptically. One-half of each lung will be used for the lung fibroblast micronucleus assay and the other half will be used for the Big Blue Mouse in vivo

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mutagenic assay. Slides or plates from 5 each from the 10 mg/m^3 RASS and DEE treated groups and the filtered air control group will be analyzed. If a high dose treated group(s) exhibits a positive response, then the slides and/or plates for the low dose group(s) will be scored.

K. Enzyme Activity

During week 4, lung, liver, and kidney samples will be collected from 6 mice/sex/group. Microsomal and cytosolic subcellular fractions will be prepared by differential centrifugation. Cytochrome P450 and glutathione-S-transferase activity will be determined.

L. Protein/DNA Adducts

Blood will be collected from 5 mice/sex/group from the adducts assay special study animals prior to terminal sacrifice. The mice will be placed in metabolism cages for a 16 hour urine collection. At terminal sacrifice samples of the lung and trachea will be collected from these animals and frozen at -80°C. The urine and tissue samples will be evaluated for protein/DNA adducts.

M. Carboxyhemoglobin

Blood will be collected from 3/sex/group selected at random from the core study animals during weeks 5, 9, and 13. Mice will be removed from the exposure chamber within one hour before the end of the daily exposure period, anesthetized with ~70% CO_2, and bled from the supra-orbital sinus.

K. Clinical Pathology Evaluations

Prior to terminal necropsy 10 mice/sex/group selected at random from the core study animals will be anesthetized with ~70% CO_2 and blood samples will be collected from the supra-orbital area into tubes containing potassium EDTA for a leukocyte differential count.

L. Lung Clearance

On the day following the termination of the 13-week RASS and DEE exposures, 18 male mice/group will be exposed to 10 mg TiO_2/m^3 for 5 consecutive days. Lung burdens of TiO_2 will be determined, using ICP-AES techniques, on 3 animals/group at 0, 1, 3, 9, 30, and 90 days following termination of TiO_2 exposures.

M. Minute Volume

Six male mice per group (one group/day) during the TiO_2 exposures. Collection of respiratory data from the plethysmographs will be conducted between 1 hour after the start of exposure and the end of the exposure period.

Tidal volume (ml) and respiration rate (breaths/min) will be monitored continuously for 10 minutes. Average tidal volume and respiration rates will be calculated and stored for all breaths occurring during each 10-second interval of monitoring. Minute volume (ml/min) will be calculated as the product of the 10-second average tidal volume and the 10-second average respiration rate. The mean and standard deviation of the minute volume for the entire 10-minute recording session will then be calculated from the 10-second average minute volumes.

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Body weights will be recorded on these mice on the day that the minute volume data are collected. If minute volume data are not collected on a scheduled weighing day, these weights will be in addition to the regular weekly body weights.

N. Proliferating Cell Nuclear Antigen

At histopathology, additional sections of nose, larynx, and lungs will be cut. Mucosal epithelial cell replication rates in these tissues will be compared by labeling the nuclei with the PC-10 monoclonal antibody and counting labeled nuclei.

XXII. POSTMORTEM OBSERVATIONS AND MEASUREMENTS

A. Necropsy

A complete necropsy will be performed on all core study mice. Findings will be recorded on an Individual Animal Necropsy Record (IANR) form. All 13-week study mice will be necropsied on the day following the last day of exposure. The recovery group will be necropsied 13 weeks after the last exposure. Mice will be killed by anesthetization with CO_2 followed by exsanguination. Necropsies will include an external examination of all body orifices, an examination of tissues/organs, and fixation in 10% neutral buffered formalin (NBF) of the following tissues:

Adrenals
Brain (medulla/pons, cerebellar cortex, cerebral cortex)
Cecum
Colon
Duodenum
Esophagus
Eyes
Femur (including joint)
Gallbladder
Harderian glands
Heart/aorta
Ileum
Jejunum
Kidneys
Liver
Lungs (trachea, larynx, tongue, pharynx)
Lymph nodes
Mammary gland/skin
Nose
Ovaries
Pancreas
Pituitary
Preputial/clitoral glands
Prostate
Rectum
Salivary glands
Sciatic nerve
Seminal vesicles/coagulation glands
Spinal cord (cervical, thoracic, lumbar)
Spleen
Sternum with bone marrow
Stomach
Testes/epididymis
Thigh muscle
Thymus
Thyroid (including parathyroids)
Tissue masses/tumors
Urinary bladder
Uterus
Zymbal's gland

B. Organ Weights

Organ weights will be recorded from all core study mice for both adrenal glands (0.001 g), brain (0.01 g), epididymides (0.001 g), heart (0.01g), kidneys (0.01g), liver (0.01 g), lung with trachea (0.01 g), spleen (0.01 g), and testes (0.01 g). Organ to body weight and organ to brain weight ratios will be calculated. Organ weights from moribund/humane sacrifices will be collected and reported, but not included in the data analysis.

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C. Histopathology

Organs/tissues collected from the filtered air control and the high concentration RASS and DEE groups will be processed to slides and stained with hematoxylin and eosin for histopathologic examination. Special stains will be used at the discretion of the pathologist. Data will be entered onto the Xybion Path/Tox System for all mice.

A complete histopathologic evaluation inclusive of gross lesions will be performed on all core study mice from the filtered air control and the high concentration RASS and DEE groups sacrificed at the end of the 13 week exposure period. Histopathologic evaluation will be conducted on gross lesions and designated tissues from all core study animals. Tissues exhibiting effects in the high concentration group(s) will be examined in the low concentration group(s) and in the animals sacrificed at the end of the recovery period. Slides may be peer reviewed by the Sponsor. A complete histopathologic evaluation will be conducted on the following tissues :

Accessory genital organs (prostate, seminal vesicles, coagulation glands)
Adrenals, right and left
Aorta (throacic)
Brain (cerebral cortex, cerebellar cortex, pons/ medulla oblongata)
Caecum
Clitoral glands
Colon
Duodenum
Epididymis
Eyes with optic nerve (if grossly abnormal)
Femur, including joint
Harderian glands
Heart
Ileum
Jejunum
Kidney, right and left
Larynx/laryngopharynx (step sections, 4 levels, laryngopharynx at the base of epiglottis)
Liver, gallbladder
Lungs (6-μm sections every 5 mm)
Lymph nodes (mandibular, mesenteric, bronchial and mediastinal)
Mammary glands
Musculature (thigh)
Nose/nasopharynx (4 levels; Young, 1981)
Oral cavity
Ovaries (mesovaries), right and left
Pancreas
Parathyroid glands
Peripheral nerve (sciatic)
Pituitary gland
Preputial glands
Rectum
Salivary glands (submandibular and sublingual)
Skin
Spinal cord (cervical, thoracic, and lumbar)
Spleen
Sternum with bone marrow
Stomach (forestomach and glandular stomach)
Testes, right and left
Thymus
Thyroid glands
Tongue
Trachea
Urinary bladder
Uterus
Zymbal's glands
All grossly visible tumors or lesions suspected being tumors

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D. Statistical Analysis

Results from this study will include incidence tables of clinical signs, gross lesions, and histopathological observations. Group means will be calculated for:

Body weight
Body weight gain
Organ weight
Organ:body weight ratio
Organ:brain weight ratio
Leukocyte parameters
Nicotine and cotinine levels
Lung clearance
Incidence of micronuclei
Incidence of mutant colonies
Enzyme activity

Any group with a sample size less than six will have only means and standard deviations calculated. Group variances for body weight, clinical pathology and organ weight data will be compared using Bartlett's test. When the differences between group variances are not significant ($p>0.01$), a one-way analysis of variance (ANOVA) will be performed. If significant differences ($P<0.01$) among the means are indicated by the ANOVA, Dunnett's multiple comparison test will be used to determine the intergroup differences. Dunnett's makes pairwise comparisons among all group means including the control groups. Significance will be declared at the 0.05 and 0.01 alpha levels.

In the event that Bartlett's test indicates significant differences between group variances for a given parameter, the mean values between the control and each concentration group will be compared using the Behrens-Fisher t-test (Satterthwaite's method will be used to adjust for degrees of freedom). Significance will be declared at the 0.05 and 0.01 alpha levels if the P value is less than alpha divided by the number of comparisons made (Bonferroni's adjustment for multiple comparisons; Miller 1981).

The percent difference in mean body weights (MBW) between treated and control animals will be calculated as follows:[1]

$$\frac{\text{MBW of Exposed Group - MBW of Control Group}}{\text{MBW of Control Group}} \times 100\%$$

E. Study Conduct and Records Retention

Documentation will be maintained in such a manner that confidentiality for the Sponsor, in all aspects of the study conduct, will be assured.

This protocol will be the controlling document. The Study Director is to be notified immediately for clarification if discrepancies occur between the protocol and the SOPs. Any changes to this protocol will be made in the following manner. If BNW initiates the change, not associated with cost, verbal (telephonic) approval will be obtained from the Sponsor followed by written documentation by BNW to the Sponsor. Any change which impacts the cost or schedule of the study will be documented in writing and approved by the Sponsor Representative's signature prior to implementation. The Sponsor may initiate modification to the protocol by telephonic authorization to BNW followed by written documentation as stated above. This study will be conducted in compliance with Good Laboratory Practice

[1]This procedure is currently in use by the National Toxicology Program, NIEHS, Research Triangle Park, NC.

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regulations, 21 CFR 58. All records required to reconstruct the study will be maintained as stipulated in 21 CFR 58.190. All paraffin blocks and wet tissues resulting from any portion of this study will be retained by BNW until 6 months after acceptance of the final report at which time they will be sent to the Sponsor. If requested by the sponsor, all microscopic slides will be submitted to the Sponsor with the final draft report. Records to be retained in study archives will be specified by the SOP entitled "Records to be Retained for Philip Morris Studies". Records that accumulate during the study will be retained at BNW until they are shipped to the Sponsor immediately prior to the termination of the contract or until the Sponsor requests transfer, whichever occurs first.

F. Draft Report

Following a Quality Assurance audit of the raw data and data tables, a complete and detailed draft report will be submitted to the Sponsor within the time frame of the contract.

G. Reference

Miller, R.G. Jr. 1981. *Simultaneous Statistical Inference.* Springer-Verlag, New York, NY.

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XXIII. BNW APPROVAL

Earl W. Morgan, DVM, ACVPM, DABT
Principal Investigator

Date

R.A. Gelman, MS
Quality Assurance Auditor

Date

XXIV. SPONSOR APPROVAL

George J. Patskan, PhD
Sponsor's Representative

Date

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APPENDIX B

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APPENDIX B

RESUMES FOR KEY PERSONNEL

"Use or disclosure of proposal data is subject to the restriction on the Title page of this Proposal."

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R: REDACTED MATERIAL

BILLY J. CHOU

Staff Scientist, Technical Group Leader, Inhalation Toxicology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B. Vet. Sci.	R	National Taiwan University
D.V.M.	R	, National Taiwan University
M.S.	Animal Nutrition	R Kansas State University
Ph.D.	Physiology	R Kansas State University

REDACTED REDACTED

Dr. Chou joined Battelle in 1984 as Principal Investigator/Toxicologist for the NTP Program. His responsibilities are:

- To be knowledgeable and up to date in all aspects of the program, including the status of toxicity test(s), recordkeeping, reporting and detailed analysis of cost for any or all functions that make up the total operation
- To be familiar with protocols to be included in studies for a particular chemical, observe animals for clinical signs and recommend dose levels for each test phase.

Previously, he was employed as Head of the Toxicology and Animal Facility, Department of Pharmacology and Toxicology, William H. Rorer, Inc. (1976-1984) and, in the same department, Senior Pharmacologist (1973-1975). His experience has included:

- Design, supervision, evaluation and reporting of toxicity and target organ toxicity (mechanism) studies involving various chemical and potential therapeutic agents in mice, rats, guinea pigs, rabbits, dogs, nonhuman primates and pigs. Routes of administering drugs included oral, intramuscular, intravenous, dermal, ocular and vaginal.
- Design and evaluation of a battery of short-term tests for detecting gene mutations, chromosome aberrations and primary DNA damage.

In his assignment as Head of Toxicology and Animal Facility, Dr. Chou supervised animal husbandry for mice, rats, guinea pigs, rabbits, miniature pigs, dogs and rhesus monkeys. He instituted standard procedures in accordance with the Animal Welfare Act of 1970 and HEW Publication (NIH) 74-23, "Guide for the Care and Use of Laboratory Animals." Under his guidance the facility was accredited by the American Association for Accreditation of Laboratory Animal Care, and was inspected by both the U.S. Department of Agriculture and, for Good Laboratory Practices, by the U.S. Food and Drug Administration.

Publications

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JOHN R. DECKER

Research Scientist, Technical Group Leader, Bioengineering and Exposure Technology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.S. Electrical Engineering R Colorado State University

Physiology R, Colorado State University (graduate study)

Physiology R Washington State University (graduate study)

Mr. Decker joined the group in 1969, and has developed a bioengineering capability within the department. He is presently Supervisor of the Toxicology Bioengineering Group.

Mr. Decker has participated in many areas of study, including biological effects of chemical aerosols, vapors and gases, biological effects of magnetic and electric fields, effects of cigarette smoke, effects of inhaled radionuclides, effects of fly ash and sulfuric acid, electrical stimulation of bone growth into porous material, effects of endogenous heat from implanted electrical and nuclear-powered sources, detection of "bends" by Doppler flow metering, detection of epilepsy in dogs by EEG analysis, and improved methods of male and female fertility control. Specific contributions include design and fabrication of a liquid vapor generation system, a cigarette smoke exposure system, a minicomputer-controlled radioisotope aerosol exposure system, equipment for a general lung-function laboratory, both magnetic field and electromagnetic radiation exposure systems, specialized electrocoagulation instruments for sterilization of both male and female reproduction systems, and a condom field testing system.

Mr. Decker has designed and constructed fully automated, computerized data acquisition and control systems for a 90-chamber inhalation toxicology laboratory and for a wind tunnel obscurant test system.

Mr. Decker is Assistant Principal Investigator for both Exposure and Sampling System Setup and Animal Exposures for NTP-sponsored inhalation exposure projects.

Before joining the Biology and Chemistry Department, Mr. Decker worked for 1 year in the Occupational and Environmental Protection Department, designing and testing radiation detection and dosimetry instrumentation.

As an Electronics Engineer in the Department of Physiology at Colorado State University , Mr. Decker's graduate work included the design and construction of biomedical instrumentation for research in subprimate neurology. During his undergraduate years Mr. Decker was also employed as an Electronics Technician at Honeywell, Denver, CO (1966-1967).

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JEFFREY A. DILL

Senior Research Scientist, Analytical Chemistry Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.S. Chemistry (1979), University of New Mexico

Ph.D. Analytical Chemistry (1983), Colorado State University

Dr. Dill joined the Department in 1987. His duties involve development and evaluation of analytical methodologies used in chemical characterizations and qualification of test atmospheres used in inhalation toxicology studies. He is currently working with formic acid and glutaraldehyde exposures.

Previously, Dr. Dill was employed by Pacific Northwest Laboratory (PNL) in waste packaging studies for nuclear waste repository investigations. Before joining PNL, he worked for Rockwell Hanford Operations as a Solution Chemistry Laboratory Team Leader. His experience was principally in inorganic analysis of natural water samples, supporting nuclear waste repository investigations.

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R: REDACTED MATERIAL

R. ANN GELMAN

Quality Assurance Specialist, Quality Assurance Unit, Life Sciences Center, Battelle, Pacific Northwest Laboratories

B.S. Foods and Nutrition (R), Carnegie Mellon University

M.S. Nutrition ; R , University of Pittsburgh

A.A. Quality Assurance R), Columbia Basin College

Ms. Gelman, who has been with Battelle since 1976, was assigned to the Quality Assurance Unit (QAU) in February 1981. She is responsible for supervising the activities of the QAU; for assuring management that projects conducted under Good Laboratory Practices (GLP) regulations for nonclinical laboratory studies are in compliance with those regulations; for assuring management that the research facility is in compliance with those regulations; for audit and surveillance activities necessary to assure compliance; for working with Project Managers (Study Directors) in setting up GLP procedures and documentation for their projects (studies); for coordinating activities during external audits by government and client representatives.

Previously (1976-1981), Ms. Gelman was a Technical Specialist in the Cell Biology Section of the Biology and Chemistry Department. She was responsible for working with staff scientists in various areas, including the toxicology of inhaled fossil-fuel-related carcinogens and of inhaled polyaminocarboxylic acids used for excorporation of radionuclides.

Before coming to Battelle, Ms. Gelman was a Senior Research Assistant in the Department of Pharmacology and Physiology, School of Dental Medicine, University of Pittsburgh (1968-1976). Her responsibilities included supervising a research laboratory which specialized in the biochemistry of trace lipids.

Prior to that time, Ms. Gelman was Senior Research Dietitian at the Clinical Research Center, Stanford Medical Center, Palo Alto, CA (1966-1968). She supervised the activities of the Dietary Department of the Center.

From 1960-1964 Ms. Gelman was Research Dietitian, Department of Biochemistry and Nutrition, Graduate School of Health, University of Pittsburgh. She planned and implemented research diets, and instructed patients regarding therapeutic diets.

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R: REDACTED MATERIAL

ANDREW W. GIESCHEN

Scientist, Analytical Chemistry Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.S. Chemistry R , Arizona State University

B.S. Microbiology (R), Arizona State University

M.S. Chemistry R Washington State University

Mr. Gieschen is currently enrolled in the Tri-Cities University Center Master's Degree program for Electrical Engineering.

Mr. Gieschen joined the section in 1987. He is involved in measurement of chemicals in support of inhalation toxicology programs. His responsibilities include preparing reports and proposals and developing experimental methods and protocols. Current projects on which he is working include inhalation exposures to chloroprene, isoprene, butadiene, HCCPD, formic acid, tetrahydrofuran, acetonitrile and glutaraldehyde.

As a Graduate Research Assistant at Washington State University (R), Mr. Gieschen performed research on the synthesis and characterization of organic compounds used to study hydrogen peroxide solvylitic rearrangements, including computer modeling of macrocycles. He has a strong interdisciplinary background in biochemical, pharmaceutical, and organic chemistry, with academic training in electrical engineering and computer programming. He has experience with flash chromatography and thin-layer chromatography, has operated the Cary UV-VIS spectrophotometer, Jeol FX 90Q NMR, Nicolet R3m/E diffractometer, Nicolet MX-90, FT-IR, and other common chemistry techniques and instruments.

He has also had extended experience with personal computers (DOS, dBASE II & III, LOTUS 1,2,3, Fortran, Pascal, BASIC, Assembly Language, Word, WordStar) and the CMS operating system.

As an undergraduate Research Assistant at Arizona State University (R), Mr. Gieschen investigated the role of tannins in the defense of plants, gaining experience in visual spectrophotometry, experiment design, and computer data management using PDP-II, Wylbur, SAS, and Minitab.

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Publication

Gieschen, A. W., B. J. Greenspan, R. B. Westerberg, T. J. Goehl, and J. H. Roycroft. 1991. Generation, monitoring, and concentration verification of PPB concentrations of glutaraldehyde for inhalation studies. The Toxicologist 11:105 (abstract).

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R: REDACTED MATERIAL

BERNARD J. GREENSPAN

Staff Scientist, Technical Group Leader, Aerosol and Inhalation Research (AIR) Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.A.	Physics	R, Clark University
M.S.	Biophysics	R I), University of Rochester Medical Center
Ph.D.	Biophysics	R University of Rochester Medical Center

Dr. Greenspan joined the Department in 1985. He is responsible for designing inhalation toxicity studies, basic aerosol research, and exposure task management for NTP and industrial clients.

Previously (1983 to 1985), he was a Postdoctoral Participant in the Radiobiology Group of the Lovelace Inhalation Toxicology Research Institute, where he was involved in studies of the toxicity of lithium combustion aerosols and of the metabolism of inhaled beryllium aerosols. From 1981 to 1983 he was a Staff Scientist in the Inhalation Department of the Union Carbide-Mellon Institute, Bushy Run Research Center. He was responsible for the design of aerosol, dust and vapor exposure systems. From 1973 to 1975 Dr. Greenspan was employed as a Technical Specialist at the University of Massachusetts Medical School. He was involved in studies on the knee-joint afferent neurons in cats and monkeys, and in examining the effects of pharmacological agents on transmission across the neuromuscular junction of rat diaphragms.

Dr. Greenspan is a member of the following affiliations:

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Publications

Grigg, P. and B. J. Greenspan. 1977. The response of primate joint afferent neurons to mechanical stimulation of knee joint. J. Neurophysiol. 40:1-8.

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TERRYL J. MAST

Staff Scientist, Inhalation Toxicology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.S. Biochemistry/Biophysics R , University of California, Davis

M.S. Agricultural Chemistry R University of California, Davis

Ph.D. Environmental Chemistry R Department of Environmental Toxicology, University of California, Davis

Postdoctoral Appointment, Developmental and Reproductive Biology (1984-1985), California Primate Research Center, University of California, Davis

Member, Graduate Faculty, Department of Toxicology, Oregon State University, Corvallis, OR

Member, Graduate Faculty, Graduate Program in Pharmacology/Toxicology, Washington State University, Pullman, WA

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Dr. Mast joined the department in 1986. Her research interests are in the area of reproductive and developmental toxicology, with emphasis on teratology, mechanisms of developmental toxicity and pharmacokinetics associated with teratologic studies. She is currently Project Manager of the NTP-sponsored Inhalation Reproductive Toxicology Program assessing the potential reproductive toxicity of industrial solvents and intermediates, and aerosols of compounds such as cadmium oxide and gallium arsenide. As Project Manager, Dr. Mast reviews the toxicological literature on the test agent, proposes the study design, and performs the developmental toxicity studies.

Dr. Mast is studying mechanisms of the developmental toxicity induced by complex mixtures in rodents and is working on an *in vitro* system to study the ontogeny of the toxic effects in the developing lung. Lung hypoplasia produced during organogenesis, after exposure to certain fractions of complex mixtures is of special interest.

Dr. Mast joined the department following 2 years of work in developmental toxicology at the California Primate Research Center, where she studied the teratology, pharmacokinetics, and placental transfer of valproic acid in nonhuman primates and rodents. Her interest in developmental metabolism and maternal-fetal pharmacokinetics led to studies on the development of hepatic xenobiotic-metabolizing enzymes in the fetal monkey. She conducted a study in rats to correlate teratological effects of the pesticide oftanol with maternal plasma kinetics, cholinesterase activity and metabolism during organogenesis. She also participated in a study that correlated plasma levels and toxic effects on the male reproductive system of dibromodichloropropane (DBCP) administered to rhesus monkeys in drinking water.

Her 6-year tenure as Lecturer in the Environmental Toxicology Department at the University of California, Davis gave her an extensive background in the occurrence and effects of environmental toxicants. During this time she taught lecture and laboratory courses in environmental and analytical toxicology to graduates and undergraduates. Her doctoral thesis work, also performed in that department, concentrated on the collection, separation, identification and mutagenicity of airborne complex mixtures produced as a result of agricultural burning.

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Dr. Mast is a member of the following professional organizations:

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PAUL W. MELLICK

Staff Pathologist, Pathology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

D.V.M. Veterinary Medicine R The Ohio State University

M.S. Veterinary Pathology R), Cornell University

Ph.D. Comparative Pathology R University of California, Davis

Dr. Mellick joined Battelle in 1987. As a staff pathologist, his duties include supervising necropsy and providing gross and microscopic pathology descriptions, documentation, data analysis and interpreting lesions in laboratory animals used in toxicology studies. He has conducted pathology evaluations for 14-day repeated-dose inhalation studies of furfuryl alcohol, nitromethane, gallium arsenide, 2-chloronitrobenzene, and 4-chloronitrobenzene; 28-day inhalation studies of ozone; 90-day subchronic inhalation studies of furfuryl alcohol, gallium arsenide, 2-chloronitrobenzene, cadmium oxide, glutaraldehyde, and isoprene; 90-day gavage studies of lewisite; 6-month inhalation toxicity studies of isoprene, and 24-month inhalation carcinogenicity studies of tetrafluoroethane. Studies listed above were conducted in either rats or mice, or both, and all except the lewisite gavage study were sponsored by the National Toxicology Program.

Dr. Mellick serves as Principal Investigator for nose-only inhalation toxicity and carcinogenicity studies of a pharmaceutical agent sponsored by a prominent pharmaceutical company. In this capacity, he has overall project management responsibility; develops proposals and study protocols; coordinates efforts of senior staff members in the disciplines of chemistry, aerosol technology, bioengineering, toxicology, animal care, pathology, health and safety, and quality assurance to ensure that all requirements of the studies are met; monitors and controls expenditures of project funds; and communicates with the sponsor concerning progress, technical concerns, and potential problems.

Dr. Mellick also served as the Principal Investigator for the NTP/HEI Collaborative Study on the Effects of Chronic Ozone Exposure. In addition to overall program management responsibility, he coordinated the efforts of ten groups of investigators from different laboratories with the Battelle staff in ten different studies designed to evaluate the toxic effects (other than carcinogenesis) of exposure of rats to ozone for 20 months.

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Dr. Mellick has completed over 21 years of active duty in the United States Army Veterinary Corps, retiring at the rank of Colonel. All assignments involved U.S. Army medical research and development activities. All positions since July 1966 were active duty military assignments.

While Deputy Commander at Letterman Army Institute of Research, Presidio of San Francisco, CA from July 1986 to October 1987, he planned, directed and managed scientifically diverse biomedical research programs with a staff of 250 and an annual budget of $14 million. He directly supervised chiefs of seven research divisions and provided second-level supervision for 20 civilian and military scientists. He also served as Pathologist-in-Charge of Good Laboratory Practices (GLP)-compliant toxicology studies.

Dr. Mellick was Chief, Division of Comparative Medicine and Toxicology, at Letterman Army Institute of Research from August 1984 to June 1986. He planned and managed research and research support activities in toxicology, pathology, and analytical chemistry, experimental surgery, and laboratory animal

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care. He also conducted GLP-compliant toxicology studies; designed and implemented multidisciplinary studies on effects of chemical warfare agents.

From March 1983 to August 1984, he was Head, Department of Veterinary Medicine, U.S. Naval Medical Research Unit, Cairo, Egypt. While there, he planned, directed and conducted research in infectious zoonotic diseases in Egypt and other Middle Eastern countries.

As Chief of the Pathology Service at Letterman Army Institute of Research from August 1976 to March 1983, Dr. Mellick conducted pathology evaluations on laboratory animals used in studies of toxicology, effects of blood replacement solutions, nutrition and experimental surgery. He organized and developed GLP-compliant toxicology research and testing capability. He also conducted a residency training program in Veterinary Pathology which prepared eight officers for successful completion of the Board Certification Examination of the American College of Veterinary Pathologists.

Dr. Mellick was Chief, Electron Microscopy Division at Letterman Army Institute of Research from July 1975 to August 1976. He conducted and directed research, service and training functions of the Electron Microscopy Division. His duties were incorporated into those of Chief, Pathology Service, described in the preceding paragraph.

He was a graduate student in Comparative Pathology, Department of Pathology, School of Veterinary Medicine, University of California, Davis, CA from August 1972 to June 1975. During that time, he studied mechanisms and pathogenesis of pulmonary injury caused by inhalation of air pollutants. This research was the basis of his Ph.D. dissertation.

From July 1970 to August 1972, he was Chief, Toxicology Division, U.S. Army Environmental Hygiene Agency, Edgewood Arsenal, MD. He conducted toxicology studies on insecticides, insect repellents, hydrogen sulfide gas, and fluorocarbons. These studies included acute, subacute and subchronic oral, dermal, ocular, and inhalation toxicology protocols and tests for teratogenesis and behavioral effects.

As a resident in Veterinary Pathology at the Armed Forces Institute of Pathology at Walter Reed Army Medical Center, Washington, DC from November 1968 to July 1970, he performed histologic evaluation of tissues from animals used to determine the safety of irradiated foods. He prepared case reports on pathology materials submitted for consultation and participated in the Veterinary Pathology training program. This training was verified by his success in the Board Certification Examination of the American College of Veterinary Pathologists.

Dr. Mellick was a Veterinary Pathologist at the National Institute of Bacteriology and Pathology, Saigon, Republic of Vietnam from October 1967 to October 1968. At that time, he conducted safety and efficacy studies on modified live-virus vaccines and bacterins for swine and poultry. He also established an animal disease diagnostic laboratory.

From August 1966 to October 1967, he was a trainee in Veterinary Pathology at the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, DC.

He was a General Practitioner from June 1964 to July 1966 at the Champlain Veterinary Clinic, St. Albans, VT where he practiced clinical veterinary medicine and surgery in large and small animals.

Dr. Mellick is a member of the following professional organizations:

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Presentations

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RODNEY A. MILLER

Staff Pathologist, Pathology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

D.V.M. Veterinary Medicine , Iowa State University, with distinction

Ph.D. Veterinary Pathology Washington State University

Dr. Miller has been with the Department as a Research Pathologist since July 1979. He has been involved in the histopathologic evaluation of rats exposed to acid aerosols and in evaluation of histologic sections of lungs, kidneys, livers, ovaries, and uteruses of rats and rabbits exposed to numerous inhaled chemicals in conjunction with teratologic studies. Dr. Miller is assigned to necropsy supervision and numerous repeated-dose, subchronic and chronic histopathology portions of the National Toxicology Program on carcinogenesis and toxicity in rodents. He has evaluated, in rats, the long-term effect of inhaled americium nitrate, and the mammary carcinogenicity of injected plutonium citrate. He has also evaluated rats and guinea pigs that inhaled solvent-refined-coal (SRC) process solvent (short-term), and rats that inhaled diesel exhaust and coal dust (short-term) after treatment (or no treatment) with porcine pancreatic elastase. Dr. Miller has examined the respiratory tracts of rats acutely exposed to fog oils and red phosphorus smoke, and has examined fetal rat lungs in which the maternal rat had been exposed to SRC products. Dr. Miller has also examined the gills of rainbow trout after the gills were exposed to volcanic ash. Dr. Miller has performed histopathologic evaluations of rat livers for induction of gamma glutamyl transpeptidase foci after exposure to SRC products. He has performed comprehensive histopathology of rats and mice exposed subchronically and chronically to a heavy distillate from the SRC-II process. He has performed limited transmission electron microscopy of the livers of the heavy-distillate-exposed animals.

Dr. Miller has been involved in necropsy and disease diagnosis of the Hanford Miniature swine breeding herd.

After practicing small animal medicine (1971-1975), Dr. Miller was a postdoctoral Research Associate, Department of Veterinary Microbiology and Pathology, Washington State University Besides instructing undergraduates in Pathology, he has had 4 years of experience in morphologic/diagnostic pathology at the Washington Animal Disease Diagnostic Laboratory, Washington State University. Much of the diagnostic work at Washington State University involved tumor diagnosis in domestic animals. His Ph.D. research concerned the interrelationship of experimental atherosclerosis and alloxan diabetes in the rabbit.

Dr. Miller has been licensed to practice veterinary medicine in Washington since 1971. REDACTED

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Publications

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HARVEY A. RAGAN

Manager, Toxicology Department, Life Sciences Center, Battelle, Pacific Northwest Laboratories

B.S. Biology, R, Washington State University

D.V.M. Veterinary Medicine R, Washington State University

Special Fellow, NIH R Hematology, University of Utah

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Dr. Ragan joined the Department as a Research Scientist in 1962 after 3 years in private practice. His research interests for the past 20 years have been concerned with the broad aspects of hematopoiesis and lymphopoiesis. Studies have been directed to alterations in these systems following insults by radionuclides, heavy metals, and physical agents. Specific investigations include radiotracer kinetics of the cellular elements of blood, iron metabolism, reticuloendothelial functions, carcinogenesis, and evaluation of immune competence. Dr. Ragan has been Principal Investigator for DOE-funded programs on the study of interrelationships between pollutant metals and nutritional deficiencies on the hematopoietic and immune systems, the clinical pathologic effects of electric fields on rodents, and the in vitro quantitation of effects of pollutants on hematopoietic stem cells; a program for EPRI on the hematologic effects of electric field exposures; and a U.S. Navy program on the hematoimmunologic effects of exposure to pulsed microwaves.

In addition to his research interests, Dr. Ragan directs the Clinical Pathology Laboratory and provides consultation and collaboration for this discipline. As a research support group, this well-equipped laboratory provides determinations of hematologic, coagulation, serum chemistry and urine parameters for most laboratory animal species. In addition, special hematologic determinations, cytochemistry and bone marrow evaluations are developed and performed as needed for specific studies.

Responsibility as Manager of Toxicology Department includes administrative control of an annual budget of >$10 million and about 16 scientists, 26 technical specialists, 25 technicians, and 10 secretaries/clerks.

For a 2-year period starting in January 1984, Dr. Ragan was Principal Investigator on multimillion dollar toxicity and carcinogenesis studies conducted by Battelle for the National Toxicology Program.

Dr. Ragan was an NIH Special Fellow in hematology under the sponsorship of Dr. George E. Cartwright at the University of Utah Medical School during 1967-1969. His research involved the interrelationships between iron and copper on erythropoiesis in young swine.

Prior to the fellowship, Dr. Ragan's research at Hanford involved clinical and toxicologic studies into the effects of radionuclides in miniature swine, miniature goats, and sheep. He was also involved in a National Heart, Lung, and Blood Institute-funded program on the chronic effects of added endogenous heat in miniature swine implanted with a heat source in the thoracic aorta.

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Dr. Ragan is licensed to practice Veterinary Medicine, Surgery, and Dentistry in Washington, and has Federal accreditation in Washington.

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ROGER A. RENNE

Staff Pathologist, Technical Group Leader, Pathology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

Pre-Veterinary R Portland State University

D.V.M. Veterinary Medicine R Washington State University

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From 1978 to the present, Dr. Renne has served as Task Leader for all pathology tasks on the NTP inhalation carcinogenesis project. He has been a participant in a number of pathology working groups for NTP-sponsored subchronic and chronic inhalation studies performed at Battelle and has participated in a number of peer reviews of pathology data from rodent inhalation carcinogenesis and toxicology studies for industrial sponsors.

From 1985 to the present, Dr. Renne has served as Pathology Task Leader for several nose-only inhalation studies of humectants and cigarette smoke in rats and hamsters for a private industrial sponsor.

From 1988 to 1990, Dr. Renne served as the Principal Investigator and Pathology Task Leader for a confidential industrial sponsor on an inhalation study investigating the toxic effects of inhaled liquid aerosols in rats.

From 1978 to 1986, Dr. Renne was Principal Investigator for a DOE-sponsored project that assayed the carcinogenic potential of crude materials, products, and chemical and boiling-point fractions of these materials from several synthetic fossil fuel technologies, utilizing chronic (2-year) skin-painting exposure of mice.

From November 1979 to April 1982, Dr. Renne was Principal Investigator on a NIOSH-sponsored project studying the long-term fibrogenic potential of four particulate materials intratracheally instilled in hamsters.

From August 1979 to November 1980, Dr. Renne was Principal Investigator of an inhalation carcinogenesis project which involved the bioassay of 15 environmental chemicals in rodents, performed at Battelle as part of the Carcinogenesis Bioassay Program of the National Cancer Institute (NTP), under Prime Contract to Tracor Jitco, Inc.

Shortly after joining the Department in 1976, Dr. Renne was Principal Investigator on several projects, including studies evaluating the fibrogenic and carcinogenic potential of particulate oil shale materials using repeated intratracheal instillation, and inhalation toxicity studies of H_2S and ammonia in rodents. He was also responsible for histopathologic evaluation of pulmonary lesions in dogs exposed to cigarette smoke, and gross and microscopic evaluation of tissues from dogs exposed to carcinogenic doses of particulate radionuclides via inhalation.

While on the staff of Experimental Pathology Laboratories (1974-1976), Dr. Renne served as a Consultant Pathologist to the Tumor Pathology Branch of the National Cancer Institute, Bethesda, MD. Specific duties included histopathologic evaluation of tissues from rodents exposed to pesticides and other environmental chemicals as part of the NCI Chemical Carcinogenesis Bioassay Program, and consultation in revising of the Systematized Nomenclature of Pathology for use in the NCI Carcinogenesis Bioassay Program.

During military service (1968-1974) Dr. Renne was a Veterinary Pathologist, Biomedical Laboratory, Edgewood Arsenal, MD (1973-1974). Dr. Renne participated in research programs determining the

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toxicity, pharmacology, and pathology of chemical compounds of military interest. He performed necropsies on laboratory animals that had been exposed to chemical compounds. He conducted detailed microscopic pathology studies in order to assess the nature and degree of histologic responses to chemical compounds or to determine the cause of death in colony animals dying spontaneously. Specific investigations of laboratory animal diseases included glomerulonephritis in laboratory rabbits, measles-virus-induced abortion and endometritis in rhesus monkeys, and tuberculosis in rhesus monkeys. He prepared reports describing and interpreting gross and microscopic alterations occurring in these animals. He conducted a formal training program in veterinary pathology acceptable to the American College of Veterinary Pathologists.

Prior to this (1970-1973), Dr. Renne was Resident in Veterinary Pathology at the same laboratory. His activities involved gross and microscopic pathology and toxicology of chemical compounds of military interest and spontaneous laboratory animal diseases. He was a Preceptee in the U.S. Army preceptorship program in Veterinary Pathology.

Dr. Renne was assigned as Veterinary Officer, Toxicology Division, U.S. Army Environmental Hygiene Agency at Edgewood Arsenal from 1968 to 1970. His responsibilities included design and conduct of research and toxicologic evaluation of chemical compounds of military interest, including gross and microscopic pathologic examination. He was also responsible for the care of a colony of laboratory animals.

From 1966 to 1968 Dr. Renne was in private veterinary practice in Albany, OR.

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STEPHEN E. ROWE

Staff Veterinarian, Life Sciences Center, Battelle, Pacific Northwest Laboratories

B.S. Agriculture (Biochemistry option; R), Purdue University

D.V.M. Veterinary Medicine R Purdue University

M.S. Pathology R , University of Michigan

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Dr. Rowe directs the Animal Health Program for the Life Sciences Center. He is responsible for development of appropriate procedures for the acquisition and maintenance of pathogen-free animals and for minimizing environmental variables. He evaluates the health of animals upon their arrival and monitors the health and environment of animals on study. Dr. Rowe utilizes clinical and histopathological examinations and the support of the Clinical Microbiology Laboratory, which he directs, to carry out these responsibilities.

As Staff Veterinarian for ongoing projects, Dr. Rowe:

- Develops and maintains diagnostic services and disease surveillance procedures
- Develops and implements a preventive medicine program and related standard operating procedures
- Provides veterinary care, including surgery, postsurgical care, and physical examinations
- Performs gross necropsy and histopathological examinations of animals in diagnosing spontaneous diseases
- Trains technical staff in procedures involving animals
- Monitors feed, water and bedding quality
- Monitors sanitation and environmental conditions in the animal facilities
- Selects or approves sources of animals and conducts pathogen screening procedures on all shipments of animals
- Provides expertise on animal care, animal health, and humane procedures in planning experiments and preparing proposals
- Evaluates experimental effects in live animals and aids in the interpretation of experimental results
- Chairs the Animal Resources Council, which is charged with planning, communicating and facilitating animal care policies and procedures in the Life Sciences Center.

Dr. Rowe also serves as the "institutional veterinarian" and is Chairman of the Animal Care Committee. As such, he is responsible for assuring Battelle's compliance with the USDA Animal Welfare Regulations, the NIH Animal Welfare Policy and other applicable regulations and guidelines concerning animal care and use. In carrying out these responsibilities (or in association with the Animal Care Committee), he:

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- Monitors animal care and use on a daily basis
- Reviews all Battelle proposals involving the use of vertebrate animals
- Reviews all ongoing research projects using animals annually
- Conducts semiannual inspections and reviews of the animal facilities and of the Animal Care and Use Program
- Provides education and training in animal welfare and in animal care and use procedures for all staff working with animals
- Provides guidelines and training in the use of analgesics and anesthetics and their appropriate application for pain control and euthanasia.

Dr. Rowe was a Postdoctoral Fellow with the Unit for Laboratory Animal Medicine at the University of Michigan Medical School from 1970-1973. During this time, and for a period of more than 1 year, Dr. Rowe had first-line responsibility for the clinical veterinary care of several hundred primates and of a diverse population of other animals used at the University of Michigan Medical School. Training also included extensive practical experience with the gross and histopathological diagnosis of diseases in laboratory animals.

From 1968 to 1970, Dr. Rowe was a Veterinary Corps Officer with the Army Environmental Hygiene Agency, Edgewood Arsenal, MD. He conducted primary irritation, sensitization and other toxicity studies in laboratory animals and directed the animal care activities of that facility.

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R. BRUCE WESTERBERG

Staff Scientist, Technical Group Leader, Analytical Chemistry Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

B.S. Chemistry R, Southern Oregon State College

Ph.D. Analytical Chemistry R, Purdue University

Dr. Westerberg joined the Department in 1980. He provides chemistry support for inhalation studies, and is presently a Chemistry Task Leader for inhalation toxicology studies. He is also Technical Group Leader for the Analytical Chemistry Group. The responsibilities of this work include development of on-line methods for monitoring exposure levels, their implementation, and studies of the possible degradation of exposure levels. Dr. Westerberg has been the Principal Investigator for several projects involving determination of trace levels of a test material and major metabolites in plasma. He has also provided chemistry support for studies of the metabolism of carcinogens in the presence of complex organic mixtures.

Dr. Westerberg has also assisted in the operation of a high-resolution mass spectrometer; this involves analyses requiring a variety of techniques: determination of elemental composition by exact mass measurements, trace analysis using fused silica column gas chromatography and selected ion monitoring, field desorption, negative ion chemical ionization, etc.

Previously (1974-1980), Dr. Westerberg was employed by E. I. duPont Chambers Works, Jackson Laboratory, as an Analytical Research Chemist. During part of that period he was responsible for the laboratory's HPLC facilities. He also upgraded the GC/MS facilities and demonstrated increased analytical capability provided by new instrumentation, with emphasis on quantitative trace analysis. This work included analysis of industrial waste waters for priority pollutants, and analysis for polychlorinated biphenyls (PCBs) in complex materials.

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Kelman, B. J., D. L. Springer, and R. B. Westerberg. 1983. Metabolic Distribution of Benzo(a)pyrene (BaP) in the Circulation of the Rodent. Presented at the Society of Toxicology Meeting, March 7-11, 1983, Las Vegas, NV.

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EARL W. MORGAN

Staff Scientist, Inhalation Toxicology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

Educational Institutions Attended:

Civilian:

New Mexico State University	Physics: R
University of Missouri-Columbia	BS, Animal Husbandry: R
University of Missouri-Columbia College of Veterinary Medicine	DVM, Veterinary Medicine: R
University of Kansas Medical	PhD Candidate (Toxicology): R

Military:

School of Aerospace Medicine Brooks AFB, TX	Veterinary Officer Basic: R
Academy of Health Sciences Fort Sam Houston, TX (correspondence): 1983-1984	Army Medical Department Officers Advanced Course
6227 US Army Reserve School Presidio of San Francisco, CA	Command and General Staff College (Seminar & Residence): R

Research Background:

Four years applied toxicology (GLP).

Three years basic toxicology (Dissertation research on going).

One year aerosol toxicology including approximately 4 months post-doctoral training.

Administrative Background:

Supervised 4-14 veterinary technicians (Air Force and Marine).

Supervised Mammalian Section, Toxicology Branch, Letterman Army Institute Research. Section included: 2 DVM's, 1 PhD, and 5 BS level investigators and 6 animal caretakers.

Owned and operated a private veterinary practice with two employees.

Dr. Morgan served as chief of the Aerosol Biology Department. Supervised 3 PhD investigators and 3 technicians. Dr. Morgan was responsible for both basic and applied research on effects, mechanism of action, and prevention or prophylaxis of toxins of biological origins through aerosol exposure. He provided

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consulting and aerosol exposure support to other investigators within the Institute and U.S. Army Medical Research and Development Command.

Dr. Morgan performed an abbreviated post-doctoral training program in aerosol biology at the Battelle Pacific Northwest Laboratories, Richland, WA (Sep-Nov 90) and University of Rochester, NY (Nov-Dec 90) under the direction of Dr. Bernard Greenspan and Dr. Gunter Oberdorster, respectively prior to assuming my duties at USAMRIID.

Description of Previous Duties:

PhD Candidate — Aug 1987 - Current
Kansas University Medical Center
Department of Pharmacology, Toxicology, and Therapeutics
Kansas City, KS

Position Description: Graduate student in toxicology at KUMC, see description of dissertation project attached to end. Plan to defend dissertation end of current semester.

Chief Mammalian Testing Section — Mar 1986 - Jul 1987
Division of Toxicology
Letterman Army Institute Research
Presidio of San Francisco, CA

Position Description: Served as Mammalian Testing Section Chief. Supervised 7 professional investigators and 6 animal caretakers. Served as investigator for toxicological studies conducted in compliance with the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) Good Laboratory Practice Regulations. Prepared protocols, Standard Operating Procedures (SOP), and reports in compliance with Good Laboratory Practice Regulations. Conducted classical acute, subchronic, and chronic applied toxicological studies to include: LD_{50}, dermal and ocular irritation, dermal sensitivity, reproductive and teratology assays, 14, 28, and 180 day feeding studies, and a 2 year carcinogenicity bioassay as well as assisted with some Ames assays. Member of LAIR Animal Use Committee. Veterinarian for Toxicology Group animals.

Principal Investigator — Jul 1983 - Mar 1986
Toxicology Section
Division of Comparative Medicine
Letterman Army Institute Research
Presidio of San Francisco, CA

Duties: Same as above except supervisory duties.

Private Veterinary Practice — Aug 1981 - Jul 1983
Richland, MO and Oklahoma City, OK

Duties: Clinical Medicine. The practice at Richland, MO was a small town general veterinarian practice. However, it was predominately large animal, beef cow/calf and dairy. The practice at Oklahoma City was a 24 hour emergency hospital. The practice was predominately companion animals. However, we also

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treated a number of exotic pets as well as some large animals. Approximately 20% of the practice was equine medicine as the practice was co-owned and located with the Oklahoma Horse Shoeing School.

Base Veterinarian — Sep 1980 - Aug 1981
Columbus AFB, MS

Duties: Clinical Medicine, Preventative Medicine and Food Hygiene.

Chief Veterinary Service — Nov 1977 - Aug 1980
Camp Pendleton MCB, CA

Duties: Clinical Medicine, Preventative Medicine and Food Hygiene for three major Marine Corps Bases in southern California.

Base Veterinarian — Jul 1976 - Nov 1977
Kunsan AFB, Korea

Duties: Clinical Medicine, Preventative Medicine and Food Hygiene for southwest Korea; area included two Air Force Bases and four Army sites.

Professional and Scientific Societies:

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Honors and Fellowships Received:

National Science Foundation Scholar in Physics, Asbury College - 1967

Deans List - New Mexico State University and University of Missouri-Columbia

American Animal Science Society Scholarship Award - 1971

Air Force Health Professions Scholarship Program

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Distinguished Graduate, Veterinary Officer Basic

AVMA Outstanding Student Award, Veterinary Officer Basic

Honor Graduate, Command and General Staff School

Expert Marksman

Air Force Commendation Medal

Army Commendation Medal

Special Appointments:

Hazardous Waste Disposal Officer while assigned at LAIR.

References:

Dr. Andrew Parkinson
Department of Pharmacology, Toxicology and Therapeutics
Kansas University Medical Center
Kansas City, Kansas 66103

Col. David R. Franz
Chief, Pathophysiology Division
U.S. Army Institute of Infectious Diseases
Ft. Detrick, Maryland 21702-5011

Dr. Richard C. Dorn
College of Veterinary Medicine
Ohio State University
Columbus, Ohio

Publications:

Papers:

Morgan E.W., Ho B., Brown L.D., Lewis C.M., Tillotson J.A., Lollini L.O., and Korte D.W. Jr.: Metabolism and Subchronic Toxicity of Nitroguanidine in the Rat. In: Proceedings of the Safety and Environmental Protection Subcommittee of the Joint Army-Navy-NASA-Air Force Interagency Propulsion Committee. Laurel, MD: Chemical Propulsion Information Agency, 1985. Note paper presented Nov 1985.

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Morgan E.W., Greenway D., and Parkinson A.: Purification of Two Rat liver Microsomal Carboxylesterases (Hydrolase A and B) With High Activity Towards *Para*-nitrophenylacetate. Archives of Biochemistry and Biophysics (paper submitted).

Morgan E.W., Greenway D., Wood G., and Parkinson A.: Regulation of Two Rat liver Microsomal Carboxylesterases (Hydrolase A and B). Archives of Biochemistry and Biophysics (paper submitted).

Morgan E.W. and Parkinson A.: Interindividual Variation and Tissue Distribution of Microsomal Carboxylesterase Activity in Humans. (In preparation).

Technical Reports:

1. Morgan E.W., Sano S.K., and Korte D.W. Jr.: Acute Oral Toxicity (LD_{50}) of Guanidine Hydrochloride in Male and Female Rats. Letterman Army Institute of Research (LAIR), Presidio of San Francisco, California Report No.204.
2. Mullen L., Morgan E.W., Lewis C.M., Wheeler C.R., and Korte D.W. Jr.: Acute Oral Toxicity of Guanidine Nitrate in Male and Female Rats. LAIR Report No. 267.
3. Hiatt G.F.S., Morgan E.W., and Korte D.W. Jr.: Dermal Sensitization of Guanidine Hydrochloride in Guinea Pigs. LAIR Report No. 210.
4. Morgan E.W., Bauserman J.W., and Korte D.W. Jr.: Primary Eye Irritation of Guanidine Nitrate in Male Rabbits. LAIR Report No. 212.
5. Morgan E.W., Hiatt G.F.S., and Korte D.W. Jr.: Acute Oral Toxicity (LD_{50}) of Guanidine Hydrochloride in Male and Female Mice. LAIR Report No 418.
6. Morgan E.W., Hiatt G.F.S., Lewis C.M., and Korte D.W. Jr.: Acute Oral Toxicity (LD_{50}) of (E)-1,2,3,4-Tetrahydro-6-Methyl-1-2-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5) in Male and Female Rats. LAIR Report No. 217.
7. Morgan E.W., Mullen L., and Korte D.W. Jr.: Primary Dermal Irritation Potential of Guanidine Hydrochloride in Male and Female Rabbits. LAIR Report No. 213.
8. Morgan E.W., Sano S.K., and Korte D.W. Jr.: Primary Dermal Irritation Potential of Nitroguanidine in Male and Female Rabbits. LAIR Report.
9. Hiatt G.F.S., Morgan E.W., and Korte D.W. Jr.: Dermal Sensitization Potential of Guanidine Nitrate in Guinea Pigs. LAIR Report No. 282.
10. Sano S.K., Morgan E.W., and Korte D.W. Jr.: Mutagenic Potential of Hydroxylamine Hydrochloride (TP046). LAIR Report.

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12. Sano S.K., Morgan E.W., and Korte D.W. Jr.: Mutagenic Potential of Nitroguanidine (TP036). LAIR Report.

13. Morgan E.W., and Korte D.W. Jr.: Primary dermal Irritation Potential of Trimethylolethane Trinitrate (TMETN) in Rabbits. LAIR Report.

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15. Morgan E.W. and Korte D.W. Jr.: Acute Oral Toxicity of Ballpowder® in Sprague Dawley Rats. LAIR Report No 350.

16. Morgan E.W., Hiatt G.F.S., and Korte D.W. Jr.: Primary Eye Irritation Potential of Ballpowder® in Male Rabbits. LAIR Report No. 352.

17. Morgan E.W., Ryabik J.R.G., and Korte D.W. Jr.: Dermal Sensitization of Ballpowder® (Olin WC 844). LAIR Report.

18. Morgan E.W., Ryabik J.R.G., and Korte D.W. Jr.: Acute Oral Toxicity (LD_{50}) of Triethyleneglycol Dinitrate (TEGDN). LAIR Report.

19. Morgan E.W., Brown L.D., Lewis C.M., Dahlgren R.R., and Korte D.W. Jr.: Fourteen-Day Subchronic Oral Toxicity Study of Nitroguanidine in Rats. LAIR Report No. 272.

20. Morgan E.W Hiatt G.F.S., and Korte D.W. Jr.: Primary Dermal and Ocular Irritation Potential of 3-Chloro-4, 4-Dimethyl-2-Oxazolidione (Compound I). LAIR Report.

21. Morgan E.W. and Korte D.W. Jr.: Primary Dermal Irritation Potential of Nitrosoguanidine in Female Rabbits. LAIR Report No. 356.

22. Morgan E.W., Justus J.D., and Korte D.W. Jr.: Acute Dermal Toxicity of Nitrosoguanidine in Rabbits. LAIR Report No. 355.

23. Morgan E.W., Justus, J.D., and Korte D.W. Jr.: Primary Dermal Irritation Potential of JA_2 Solid Propellant in Rabbits. LAIR Report No. 413.

24. Morgan E.W. and Korte D.W. Jr.: Acute Dermal Toxicity (MLD) of Triethyleneglycol Dinitrate (TEGDN). LAIR Report No. 342.

25. Morgan E.W. and Korte D.W. Jr.: Acute Dermal Toxicity of Trimethylolethane Trinitrate (TMETN) in Rabbits. LAIR Report No 347.

26. Morgan E.W., Frost D.F. Wheeler C.R., and Korte D.W. Jr.: Acute Oral Toxicity of JA_2 Solid Propellant in ICR Mice. LAIR Report No. 414.

27. Morgan E.W., Brogden J.D., and Korte D.W. Jr.: Primary Eye Irritation Potential of JA_2 Solid Propellant in Rabbits. LAIR Report No. 415.

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28. Morgan E.W. and Korte D.W. Jr.: Acute Oral Toxicity of Nitrosoguanidine in Sprague Dawley Rats. LAIR Report No. 354.

29. Morgan E.W., Wheeler C.R. and Korte D.W. Jr.: Acute Oral Toxicity of Nitrosoguanidine in ICR Mice. LAIR Report No. 354.

30. Morgan E.W., Justus J.D., Frost D.F., and Korte D.W. Jr.: Dermal Sensitization Potential of Nitrosoguanidine in Guinea Pigs. LAIR Report No. 357.

31. Morgan E.W., Pearce M.J., Zaucha G.M., Lewis C.M., Makovec G.T., and Korte D.W. Jr.: Ninety-Day Subchronic Oral Toxicity Study of Nitroguanidine in Rats. LAIR Report No. 306.

32. Magnuson D.K., Morgan E.W., and Korte D.W. Jr.: Primary Dermal Irritation Potential of Physostigmine Salicylate. LAIR Report No. 331.

33. Frost D.F., Morgan E.W., Letellier Y.C., Pearce M.J., Ferraris S, Smith C.D., Zaucha G.M., and Korte D.W. Jr.: Ninety-Day Subchronic Oral Toxicity Study of Nitroguanidine in Mice. LAIR Report No. 319.

34. Morgan E.W., Zaucha G.M., Waring P.P., Letellier Y.C., Seewald J.B., Clifford C.B., and Korte D.W. Jr.: Ninety-Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats. LAIR Report No. 435.

35. Morgan E.W., Zaucha G.M., Waring P.P., Letellier Y.C., Seewald J.B., Clifford C.B., and Korte D.W. Jr.: One Hundred Eighty Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats. LAIR Report No. 441.

36. Morgan E.W., Zaucha G.M., Bowman P., Schuschereba S.T., Waring P.P., Letellier Y.C., Seewald J.B., and Korte D.W. Jr.: Ninety-Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats - Electron Microscopy Study of Neuromuscular Junctions. LAIR Report No. 436.

Abstracts:

1. Morgan E.W., Wood G., Greenway D.J., and Parkinson A.: Developmental Changes in the Levels of a Rat Liver Microsomal Carboxyesterase (Hydrolase A). The Toxicologist 1989;9:39. Note paper presented 28 Feb 89.

2. Lewis C.M., Morgan E.W., Brown L.D., Pearce M.J., Zaucha G.M., Makovec G.T., and Korte D.W. Jr.: 90-Day Oral Subchronic Toxicity of Nitroguanidine in Rats. The Toxicologist 1989;9:425. Note poster presented 28 Feb 89.

3. Morgan E.W. and Parkinson A.: Comparison of the tissue distribution of two isozymes of rat liver microsomal carboxyesterase (hydrolases A and B). The Toxicologist 1990;10:127. Note paper presented 14 Feb 90.

4. Yan B, Morgan E.W., and Parkinson A.: Immunocytochemical localization of two carboxyesterases (hydrolases A and B) in rat liver, testis, and kidney. The Toxicologist 1990;10:323. Note poster presented 16 Feb 90.

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5. Parkinson A., Morgan E.W., and Yan B.: Purification and characterization of two rat liver microsomal carboxyesterases; studies on their regulation and tissue distribution In: Proceedings of the Eighth International Symposium on Microsomes and Drug Oxidations. Karolinska Institute, Stockholm, Sweden, 1990. Note presented Jun 90.

6. Yan B, Morgan E.W., Parkinson A.: Esterase activity in human liver, kidney, and testis. The Toxicologist 1991;11:228. Note poster presented on 28 Feb 90.

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NAZLI EGILMEZ-REYNOLDS

Senior Research Scientist, Aerosol and Inhalation Research, Toxicology Department, Battelle, Pacific Northwest Laboratories

Ph.D Chemistry R , School of Science and Engineering, University of Essex, England.
M.Sc Chemistry R , School of Science and Engineering, University of Essex, England.
B.Sc Chemical Engineering R , Aegean University, Turkey.

CAREER HISTORY AND ACCOMPLISHMENTS

*University of Louisville; Chemistry Department (August 1988 - May 1991)

Visiting Assistant Professor

Full-time Instructor of General Chemistry (100 and 200 level) lectures and laboratories.

- Taught Introductory chemistry course to a mixture of students (majors and non-majors) for seven consecutive semesters, totalling some 1250 students in thirteen sections. Used instructional aids frequently.
- Organized and supervised 100 and 200 level laboratory courses on General Chemistry as the Senior Instructor. Supervised a total of 16 teaching assistants from six different countries.
- Taught Introductory Analytical Chemistry course with lecture and laboratory.
- Formed close contacts with the students, providing necessary counseling and additional help in the form of study sessions outside office hours (see the letter from the Board of Trustees and the student evaluations enclosed).
- Prepared a graduate level course on Aerosol Science and Technology upon an invitation by the Chemical Engineering Department of Speed School of U of L.
- *Self-employed Aerosol Scientist (July 1987 - Present)

Scientific Consultant on Aerosol Science and Technology/Tobacco Smoke

Advisor on the formation, measurement, filtration and behavior of Aerosol Systems and their interaction with humans and the environment. The following companies have been clients:

- British-American Tobacco Co., Hamburg, Germany (BAT Cigaretten Fabriken Gmb)
- Brown and Williamson Tobacco Co., Louisville, USA.
- C.A. Blockers, Inc., Louisville, USA.

*British-American Tobacco UK & Export Ltd., Southampton, England (1983-1987)

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Research Scientist - Product Research Section

Responsible for the Aerosol Laboratory; Chief Aerosol Scientist for the BAT Group worldwide.

- Developed and executed work programs on aerosol generation and behavior inside the cigarette, filters, human upper airways and environmental rooms.
- Provided an expert advisory service to complement the needs of other BAT Research Centers and R&D Sections.
- Coordinated research with associated laboratories in Louisville (USA), Hamburg (Germany) and Montreal (Canada).
- Identified and devised instrumentation and data-logging facilities; organized, conducted and interpreted experimental studies and communicated the results and implications throughout BAT by writing reports and giving verbal presentations.
- Developed synthetic smoke generation techniques and used model aerosols to investigate the relation between smoke taste and its aerosol characteristics.
- Produced guidelines and provided advice on the design of new products. Worked on the concept of alternative products and designed two hand-held delivery systems.
- Used specialized aerosol equipment by TSI, PMS, and ROYCO, interfaced with Apple and IBM PCs, in the generation and counting of particles.

*University of Essex, Colchester, England (1980-1983)

Research Assistant, Department of Chemistry

Reported to the Director of the Aerosol Lab., Prof. C.N. Davies.

- Developed and characterized a synthetic aerosol generator of $CaCO_3$ in nanometer particle radius.
- Performed coagulation experiments using monodisperse and polydisperse aerosols at varying particle sizes and concentrations, demonstrating the large discrepancy between theory and experiments.
- Developed a new theory of aerosol coagulation for submicron aerosol particles in the light of experimental results.
- Evaluated the losses in a Nolan-Pollack Counter and demonstrated the validity of its calibration.
- Reviewed papers as a referee for the Journal of Aerosol Science.

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JOHN Y. YOUNG

Health and Safety Officer, Inhalation Toxicology Technical Group, Toxicology Department, Battelle, Pacific Northwest Laboratories

Education:

University of Washington, Seattle, WA

1980 Master of Science in Public Health (Industrial Hygiene)
Thesis Title: Personnel Exposure to Methylmethacrylate in Operating Theaters
1971 Bachelor of Science (Preventive Medicine)

Certifications:

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Summary of Experience:

Mr. Young has planned and implemented industrial hygiene and environmental protection program for conduct of animal studies involving toxic and potentially carcinogenic chemicals. He has twenty years of military service as a U.S. Army environmental science officer specializing in industrial hygiene, with experience in industrial hygiene research and consulting, rural sanitation projects and training, military installation environmental compliance, and health surveillance activities. Extensive experience in the past six years in conducting toxic hazard research and in administering an occupational health research program for the U.S. Army.

Professional Memberships:

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U.S. Army Biomedical Research and Development Laboratory, Fort Detrick, MD

1990-1992: CHIEF, OCCUPATIONAL HEALTH RESEARCH BRANCH

- Managed a research branch of an Army research and development laboratory, responsible for planning research projects and programming resources and budget for both in-house and extramural occupational health research.
- Supervised 9 research scientists involved in medical research to study the health effects of military-unique chemical hazards, to conduct exposure assessment studies on soldiers' exposures to smoke and weapons combustion products, and to develop innovative techniques for military field water and sanitation.

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- Interacted extensively with Army medical units and major Army system and material developers, and served as a consultant to these organizations on industrial hygiene related matters, and

- Served as a Source Selection Board member involved in the evaluation and selection of contractors for Army system and material development programs.

1986-1990: ENVIRONMENTAL SCIENCE OFFICER/INDUSTRIAL HYGIENIST

- Managed and conducted both in-house and extramural occupational health research projects, served as a research team leader, and solicited/coordinated field support

  - to evaluate soldiers' exposure to:

    - weapons combustion products inside armored vehicles
    - deliberately-generated smoke in military field training
    - rocket and missile launch combustion products

  - to characterize:

    - physical/chemical compositions of propellant combustion products
    - particle size distribution of experimental obscuration smoke
    - dispersion modeling of obscuration smoke

  - to develop data base on:

    - medical criteria for military respiratory protection
    - training scenarios involving the use of obscuration smoke

- Provided consultation services to U.S. Army Missile Command on toxic hazards associated with major weapon design and procurement. This involved defining industrial hygiene air sampling procedures during prototype weapon testing, reviewing contractor's design proposals, and establishing acceptability criteria regarding occupational health protection issues.

- Maintained equipment calibration, planned equipment requirements for future industrial hygiene research, prepared various research protocols and developed quality control procedures to improve this laboratory's occupational health research program.

7th Infantry Division (Light), Fort Ord, CA

1984-1986: COMMANDER, 172D MEDICAL DETACHMENT

- Commanded a preventive medicine detachment of 11 personnel. Duties included administrative personnel actions, combat-readiness training, and professional development of assigned personnel.

- Supported the 7th Infantry Division regularly on field training maneuvers to monitor and improve sanitary conditions of field water supplies, food services, and bivouac areas. Also supported the 7th Infantry Division to process units being deployed overseas.

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AWARDS

- Research Assistantship (1980-1983) offered by the SERC of Britain
- British Council Award (1979-1980)
- Fulbright Scholarship (1978)

MEMBERSHIPS

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PUBLICATIONS

Egilmez, N. and Davies, C.N. (1986) "Aerosols: Formation and Reactivity", Chapter 6, Pergamon Press, London, 453.

Davies, C.N. and Egilmez, N. (1986) "Nolan-Pollack Condensation Nucleus Counter", Letter to the Editor, Aerosol Science and Technology, 5, 117.

Davies, C.N. and Egilmez, N. (1984) "An Investigation into the Loss of Particles by Diffusion in the Nolan-Pollack CNC", Journal of Aerosol Science, 15, 177-181.

Egilmez, N. and Davies, C.N. (1982) "Coagulation of Fine Aerosol", Proceedings of Royal Society of London, A 380, 99.

Egilmez, N. and Davies, C.N. (1981) "Coagulation of Fine Aerosols", Journal of Aerosol Science, 12, 184.

RAT REPORTS (1983-1987; restricted for open publication):

- Review of Studies on Cigarette Smoke Aerosol Formation
- Generation of Two-Component, Relatively Monodisperse Aerosols
- Evaluation of a Patented Noncombustible Cigarette
- Aerosol Particle Formation During the Heating of Tobacco
- Joint Aerosol Studies in Chemosensory Research
- Ambient Smoke Aerosol Characterization
- Smoke Aerosol Characterization of Some Slim and Low-tar Cigarettes from the U.S. Market
- Development and Calibration of a Synthetic Aerosol Generator

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- A Preliminary Study of Aerosol Characteristics Inside a Glass Model of the Human Upper Airways
- Aerosol Characterization of Smoke From Cigarettes Tipped With Extreme Design Filters
- Sensory Perception Assessment of Synthetic Aerosols

PRESENTATIONS

SECOND INTERNATIONAL AEROSOL CONFERENCE, West Berlin, Germany, September 22-26, 1986; "The Coagulation of Fine Aerosols".

EUROMEC COLLOQUIUM, University of Cambridge, Cambridge, England, April 1985; "Coagulation of Fine Aerosols Alone and When Mixed With a Coarse Aerosol".

EUROMEC COLLOQUIUM, University College, London, England, September 1982; "Coagulation of Aerosols--a Discussion of the Various Regimes of Coagulation and Their Experimental Basis".

INTERNATIONAL AEROSOL CONFERENCE, Schmallenberg, Germany, September 20-24, 1980; "Coagulation of Submicron Aerosols".

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- Provided a monthly 1-week training course on field sanitation to assigned units in the 7th Infantry Division, and to other active and reserve military units in the Monterey area.

U.S. Army Pacific Environmental Health Engineering Agency, U.S. Army in Japan

1980-1984: CHIEF, INDUSTRIAL HYGIENE DIVISION

- Performed administrative functions of a small industrial hygiene division and supervised 2 industrial hygienists and one industrial hygiene technician.
- Planned and programmed resources to implement an industrial hygiene surveillance/support program for Army installations in Japan, Korea, Kwajelein Islands, and Hawaii. Also served the Department of Defense, U.S. Air Forces, U.S. Navy, and U.S. Coast Guard as needed in Japan, Korea, Guam, Yap, and the Philippines.
- Conducted comprehensive industrial hygiene surveys and hearing conservation surveys on all supported installations by following a schedule of at least one visit every 2 years.
- Received requests and conducted industrial hygiene special studies on specific health hazards such as asbestos, benzene, mercury, lead, carbon monoxide, pentachlorophenol, polychlorinated biphenyls, hexachloroethane, and noise.
- Established a laboratory to identify bulk asbestos samples using the polarized light microscopy technique.

Letterman Army Medical Center, Presidio of San Francisco, CA

1974-1978: ENVIRONMENTAL SANITARIAN

- Supervised up to 18 environmental health technicians and reported to a preventive medicine physician.
- Provided the full spectrum of environmental health surveillance and support in the Army and Department of Defense facilities in Northern California. Support services included drinking water supply surveillance; air pollution source monitoring; sanitary inspection of food service/ice-making facilities; barber/beauty shops; child care facilities; detentional cells; solid waste disposal planning; hospital infection control; operating room clean air monitoring; routine industrial hygiene support; pesticide monitoring; and health status documentation and reporting.

1st Special Forces Group, U.S. Army in Okinawa

1973-1974: PUBLIC HEALTH TEAM LEADER, CIVIL AFFAIRS

- Planned special forces civil affairs sanitation projects.
- Visited remote villages in the Philippines to provide classroom instructions to local doctors, nurses, sanitarians, and school teachers on sanitation and disease prevention.

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- Constructed water catchment tanks to protect village water supplies.
- Constructed and installed water-sealed toilet facilities to provide a sanitary means for human fecal disposal.

Academy of Health Sciences, U.S. Army, Fort Sam Houston, TX

1972-1973: PREVENTIVE MEDICINE INSTRUCTOR

- Served as an instructor and advisor for students attending the Army Preventive Medicine Basic (91S10) Course.
- Prepared lesson plans for the 91S10 and the Advanced (91S20) courses.
- Provided classroom support when not involved in class instruction.

RECENT PUBLICATIONS:

Technical Reports:

Young, J.Y., D.A. Smart, J.T. Allen, D.L. Parmer, A.B. Rosencrance, E.E. Brueggemann, and F.H. Broski. September 1989. Field exposure of chemical school students and cadre to fog oil and hexachloroethane (HC) smokes. U.S. Army Biomedical Research and Development Laboratory Technical Report 8908. Defense Technical Information Center Publication No. AD A225008.

Eaton, J.E. and J.Y. Young. January 1989. Medical criteria for respiratory protection in smoke: the effectiveness of the military protective mask. U.S. Army Biomedical Research and Development Laboratory Technical Report 8902. Defense Technical Information Center Publication No. AD A204303.

Smart, D.A., D.L. Parmer, J.Y. Young, W.G. Palmer. In press. The relationship between doctrine for Army tactical smoke use and exposure potential: priorities for conducting smoke exposure assessment studies. U.S. Army Biomedical Research and Development Laboratory Technical Report 9115.

Proceedings:

Young, J.Y., D.A. Smart, D.L. Parmer, J.T. Allen, and S.H. Hoke. April 1988. Measurement of field exposure to fog oil and hexachloroethane smokes. In Proceedings of the smoke/obscurants symposium XII, ed. W.M. Farmer and W. Klimet. Aberdeen Proving Ground, MD: Office of the Program Manager for Smoke/Obscurants.

Young, J.Y. September 1988. Exposure assessment related to smoke/obscurants. In Proceedings of the tri-service pulmonary research review and analysis in Denver, Colorado. Fort Detrick, MD: U.S. Army Medical Research and Development Command.

Young, J.Y. September 1988. Evaluation of breathing-zone exposure to AAWS-M exhaust combustion products. In Proceedings of the tri-service pulmonary research review and analysis in Denver, Colorado. Fort Detrick, MD: U.S. Army Medical Research and Development Command.

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BUSINESS
PROPOSAL

COST ELEMENT INFORMATION

DIRECT LABOR

Direct labor costs are based on average charge-out rates for specific job categories.

LABOR OVERHEAD

Building and Utilities

The estimated rates per direct labor hour for FY 1993 through FY 1997 are $6.85, $6.90, $7.40, $7.20, and $7.30, respectively. Building and Utilities are costs for occupying U.S. Department of Energy (DOE) or Battelle facilities. Typical costs include utilities, building operations, janitors, maintenance, insurance, and taxes. The rates have been approved in our Indirect Cost Rate Agreement with the Department of Energy.

Organizational Overhead

Organizational Overhead for technical organizations represents costs for management, supervision, and administration of technical departments. Organizational Overhead also includes costs for research equipment such as small tools, lab supplies, laundry, decontamination/waste disposal, maintenance, and expenses associated with Battelle owned equipment with an initial cost less than $50,000. Also included is a factor for reimbursement to the Government for use of DOE owned equipment with an initial cost less than $50,000 for work performed under Contract DE-AC06-76RLO-1831.

Organizational Overhead for non-technical organizations represents costs for department management and support. These costs are accumulated in an intermediate cost pool and are allocated to cost objectives at a predetermined rate per direct labor hour.

TRAVEL

Airfare rates have been estimated utilizing quotes from local travel agencies. Subsistence costs (meals and lodging) have been estimated using per diem rates published in the Federal Travel Regulations. Travel costs have been escalated at an annual rate of 5.0 percent.

OTHER DIRECT COSTS

BNW Procurement Services

Procurement Service Charge includes costs for procuring and receiving purchased items. For estimating purposes, an average service charge of 10% has been applied to materials (plus escalation).

Actual Procurement service charges are as follows:

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Purchase Order Amount	Charge
$100 and under	$50
Next $4,900	10%
All Over $5,000	5% (maximum of $5,290)

Subcontracts & Consulting Services
Subcontracts and Consulting service charge includes costs for placing and administering subcontracts and consultants. Subcontracts & Consulting service charges are estimated on the following basis: 8.0 percent of the total cost per subcontract up to a maximum of $25,000 per fiscal year.

Other Direct Costs
The cost of certain centralized services such as duplicating, technical information, computer usage, etc., are accumulated in an intermediate cost pool and are allocated based on the actual usage of the services provided by each center.

Special Purpose Equipment

Battelle-Owned Equipment
Costs associated with major items/systems of Battelle-owned equipment (in excess of $50,000 initial cost) are accumulated in an intermediate cost pool and allocated at a predetermined usage rate for each item.

Government-Owned Equipment
The estimated cost of Government-owned equipment usage is based on reimbursement rates established by contractual agreement between BNW and the Department of Energy. (Contract No. DE-AC06-76RLO-1831)

Cost of Facilities Capital (CAS 414)
The current estimated rates are $.87 per direct labor hour for personnel located in Battelle buildings, and $.30 per direct labor hour for personnel located in Department of Energy (DOE) buildings. The rates have been approved in our Indirect Cost Rate Agreement with the Department of Energy.

STORES OVERHEAD
The estimated cost for stores overhead is based upon a Westinghouse Hanford Company rate of 15.2 percent of store items.

GENERAL AND ADMINISTRATIVE EXPENSE
G&A includes general functions such as Accounting, Legal, and Personnel department costs, and costs for bid and proposal, selling, IR&D, contract administration, etc. G&A is allocated at the estimated rate of 45.0 percent of value added to final cost objectives.

ANIMAL RESOURCE CENTER
The Animal Resource Center (ARC) is a service center within the Toxicology Department. The ARC is responsible for routine animal

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care, animal health and management of experimental animals. The costs associated with this activity are accumulated in an intermediate cost pool and allocated to cost objectives at predetermined rates by the type of housing provided.

These rates incorporate costs for basic animal care, including costs associated with basic animal health, food, materials and equipment depreciation and maintenance cost. Basic animal care consists of the labor for all routine animal care: feeding and watering the animals; cleaning the rooms housing the animals, hallways, and cages; and supervision of the technicians and management of the Animal Resource Center. Basic health care of the animals is defined as routine monitoring of sanitation, water quality, feed and bedding, clinical observation for infectious disease and the initial health screening. Costs associated with activities above the basic level of animal care service (such as non-stock cage board), are treated as direct costs.

OVERTIME POLICY

The responsibilities of exempt staff members cannot always be met within regular work schedules, and extra time and effort is taken into consideration in determining base salary ranges for all positions as well as in the extra vacation allowance for exempt staff. However, when scheduled work time requirements beyond 40 hours per week are regular, consistent, and clearly in excess of that reasonably expected for the position, overtime payments for exempt staff members will be considered. Nonexempt staff members will receive overtime and premium pay for their overtime work.

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R: REDACTED MATERIAL

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PROVISIONS FOR CONTRACTS UTILIZING GOVERNMENT-OWNED FACILITIES AND EQUIPMENT, OR CERTAIN UNREPORTED U. S. DEPARTMENT OF ENERGY INFORMATION

It is planned that the work, or a portion thereof, to be performed hereunder will be performed at the Pacific Northwest Laboratory (hereinafter called the Laboratory), owned by the U. S. Department of Energy (hereinafter called DOE) operated for DOE by BATTELLE under Operating Contract DE-AC06-76RLO 1830 (hereinafter called Operating Contract), and used by BATTELLE for its own account under and subject to the Use Permit Contract DE-AC06-76RLO 1831 (hereinafter called Use Permit). Therefore, performance of the work hereunder shall be contingent upon the continuing availability to BATTELLE of the Government facilities and property, and the personnel necessary to conduct the work. Neither BATTELLE, nor the Government, nor DOE, nor their officers, employees, or authorized representatives shall be liable for any loss sustained by the SPONSOR, or others, where such loss is directly or indirectly attributable to the lawful exercise of the Government's right of control over health and safety at the Laboratory, or to suspension or cessation of activities under this agreement at the request of the Government pursuant to the Use Permit. The following applicable provisions of the Use Permit must be incorporated into any contract resulting from this proposal.

"8. PATENTS

A. (1) With respect to any invention or discovery conceived or first actually reduced to practice after September 30, 1979, by BATTELLE or its employees or consultants or by the employees or consultants of organizations sponsoring work at BATTELLE in the course of or under any agreement or activity undertaken pursuant to this Use Permit in which scientific or technical information and data developed by BATTELLE in the performance of work for DOE under the Operating Contract, but not reported to DOE on an unrestricted basis, (hereinafter referred to as "DOE Information and Data"), were specifically necessary for the conception or first actual reduction to practice of any invention or discovery, the Government, as represented by DOE, reserves a nonexclusive, irrevocable, royalty-free license for U. S. governmental purposes in any such invention or discovery and any patent application or patent that may result; provided, however, that nothing herein shall be deemed to modify or alter DOE's rights with respect to any invention or discovery made or conceived in the course of or under the Operating Contract. For purposes of this Article, scientific or technical information and data which are obtained by BATTELLE other than through its performance of the Operating Contract, or which are published, shall not be deemed to be "DOE Information and Data." To the extent necessary to enable DOE to determine

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the Government's rights under this Article, BATTELLE shall afford DOE the right to inspect the original records of inventions conceived or first actually reduced to practice after September 30, 1979, in the course of or under any arrangement or activity undertaken pursuant to this Use Permit; provided that no original records pertaining to work sponsored by third parties (other than BATTELLE affiliates or subsidiaries) shall be made available without the SPONSOR's consent which will not be unreasonably withheld, but if withheld then arrangements shall be made between counsel for BATTELLE and DOE for a review, at BATTELLE facilities, of the original record of any such invention and directly related information, with such records treated as proprietary data in accordance with the provisions of Article 10 for purposes of this review.

(2) BATTELLE shall report any invention or discovery covered by A (1) above within six months after conception or first actual reduction to practice and will advise DOE, within six months of such reporting, as to whether BATTELLE or the SPONSOR intends to file a United States patent application with respect to such invention or discovery; provided, however, if BATTELLE or the SPONSOR advises that neither desires to file, DOE may file any patent application, domestic or foreign, as it determines appropriate. If BATTELLE or the SPONSOR does not file a patent application within one year of reporting such invention or discovery, DOE, if it desires to file any patent application, will so notify BATTELLE and if BATTELLE or the SPONSOR does not file a patent application within 60 days after date of such notification, DOE may file any patent application, domestic or foreign, as it determines appropriate. If DOE files a patent application, all right, title and interest in and to such invention or discovery shall be assigned to DOE, subject to retention by BATTELLE or the SPONSOR, as the case may be, of at least a nonexclusive, irrevocable, royalty-free license for its own uses. With respect to any such filing, BATTELLE agrees that it will execute all documents and do all things necessary and proper to assist DOE and will use its best efforts to secure from its employees, the SPONSOR, and the inventor or inventors the execution of all documents and to have them do all things necessary and proper to assist DOE.

B. No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by BATTELLE or its employees and consultants and employees and consultants of the SPONSOR with respect to any invention or discovery based on said "DOE Information and Data" to the extent described in A (1) above in the course of or under any arrangement or activity undertaken pursuant to this Use Permit.

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C. Except as otherwise authorized in writing by DOE, BATTELLE will obtain patent agreements to effectuate the provisions of paragraphs A and B of this Article from all BATTELLE employees or consultants, or employees or consultants of SPONSORS who perform any part of the work under this Use Permit while assigned to work at the Government-owned facilities, or while utilizing the Government-owned property or "DOE Information and Data," except nontechnical personnel, such as clerical employees and manual laborers.

9. ACCESS AND TECHNICAL DATA

A. To the extent necessary to fulfill the responsibilities of DOE under any law or regulation, or for the purposes of determining compliance with the terms of this Use Permit, DOE, at all reasonable times, subject to Article 10, shall have access to all or any part of the Government-owned facilities and shall have the right to inspect all activities conducted therein; provided, however, DOE's right to inspect shall not include the right to obtain technical data except as hereinafter provided.

B. The Government shall have the right to use for Governmental purposes any information or knowledge contained in any drawings, sketches, designs, data, specifications, technical and scientific data, photographs, negatives, reports, findings, recommendations, and memoranda of every description (all of which are hereinafter included in the term "technical data") made in the course of or under any arrangement or activity undertaken hereunder which specifically results from the use of said "DOE Information and Data."

C. BATTELLE shall furnish to DOE, without charge, one copy of any technical data as to which the Government has rights under B above. To the extent necessary to enable DOE to determine the Government's rights under this Article, DOE shall have the right to inspect the technical data specifically resulting from the use of said "DOE Information and Data" which is made in the course of or under any arrangement or activity undertaken hereunder, provided that no proprietary information of a SPONSOR (other than BATTELLE subsidiaries and affiliates) shall be made available without the SPONSOR's consent, which will not be unreasonably withheld.

D. When furnishing any technical data referred to in Paragraph C above, BATTELLE or the SPONSOR, as the case may be, will make reasonable efforts to identify any invention made by BATTELLE or the SPONSOR if not previously reported.

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